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- Substituted benzazepines, their preparation and pharmaceutical compositions containing them.
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Description

BACKGROUND OF THE INVENTION

This invention relates to 1- or 5-substituted-2,3,4,5-tetrahydro-1H-3-benzazepines, their preparation and to pharmaceutical compositions containing them. The compounds have valuable pharmaceutical properties in the treatment of psychosos, depression, pain and hyportension.

Substituted 1-phenyl-2,3,4,5-tetrahydro-1H-3-benzarepines have been described in the art. For example, see U.S. Patents 3,333,192, 3,091,338, 4,011,319, 4,284,555 and 4,477,378 as well as British Patent 10,1118,688. The activities discussed for the compounds disclosed in these patents include anti-bacterial effects, central nervous system effects and hypotensive effects.

Weinstock et al. in <u>Drugs of the Future</u>, Vol. 10, No. 8, pp 645-697 (1985) discuss the profound effect that 1-phenyl substituents have on the dopaminergic activity of certain types of benzazepines. See Table II on page 888.

European Patent Application EP-A-0 096 838) discloses certain 1-aryloxy substituted 2.3,4,5-tetrahydro-Davazepines having H and/or alkoxy substituents in the 7- and 8-positions thereof. These compounds are disclosed as having utility in the treatment of depression.

SUMMARY OF THE INVENTION

It has now surprisingly been found that certain novel benzazepines lacking such a 1-phenyl substituent provide good anti-dopaminergic activity, in particular, showing surprising selectivity for the D-1 subclassification of dopaminergic receptors. Accordingly, in one of its aspects, the present invention provides benzazepines of the structural formula i:

$$R^4$$
 R^5
 R^5
 R^5
 R^5

as and the pharmaceutically acceptable salts thereof, wherein: a compound having the structural formula !

and the pharmaceutically acceptable salts thereof, wherein:

represents -XR⁶, -CH₂R⁸, cycloalkyl having 3 to 8 carbon atoms, cycloalkenyl having 5 to 8 carbon atoms.

or pyrrolyl;

represents -H or R¹ and R² together represent alkanediyl being a divalent, straight or branched hydrocarbon chain having 1 to 6 carbon atoms;

P3 represents H, or straight or branched alkyl having 1 to 6 carbon etoms; R4 represents H, halo, straight or branched alkyl having 1 to 6 carbon atoms, haloaikyl being a straight or branched alkyl having 1 to 6 carbon atoms substituted with 1 to 5 halo groups, or alkoxy (wherein the alkyl portion is a straight or branched alkyl having 1 to 6 carbon etoms); R5 rapresents -OR10, -N(R9 to or -O+C(R7 to OCOR13; represents H, straight or branched alkyl having 1 to 6 carbon atoms, cycloalkyl having 3 to 8 carbon atoms, cycloalkenyl having 5 to 8 carbon atoms, aralkyl (wherein the arvi portion is a unsubstituted or substituted phenyl wherein substituted phenyl represents phenyl mono-or di-substituted by alkyl, hydroxy, alkoxy, alkylthio, halo, trifluoromethyl or combinations thereof and the alkyl portion is a straight or branched alkyl having 1 to 6 carbon atoms), heteroarylalkyl (wherein the heteroaryl portion is an aromatic heterocyclic group having at least one O. S and/or N atom and the alkyl portion is a straight or branched alkyl having 1 to 6 carbon atoms), haloalkyl being a straight or branched alkyl having 1 to 6 carbon atoms substituted with 1 to 5 halo groups, straight or branched alkenyl having 1 to 6 carbon atoms, alkynyl having 2 to 6 carbon atoms, cycloalkylalkyl (wherein the cycloalkyl portion is a cycloalkyl having 3 to 8 carbon atoms and the alkyl portion is a straight or branched alkyl having 1 to 6 carbon atoms), cycloalkenylalkyl (wherein the cycloalkenyl portion is a cycloalkanyl having 5 to 8 carbon etoms and the alkyl portion is a straight or branched alkyl having t to 6 carbon atoms), or alkoxyalkyl (wherein both alkyl portions are straight or branched alkyls having 1 to 6 carbon atoms); represents H, or straight or branched alkyl having 1 to 6 carbon atoms; R8 represents cycloalkyl having 3 to 8 carbon atoms, cycloalkenyl having 5 to 8 carbon atoms, cycloalkylalkyl (wherein the cycloylkyl portion is a cycloalkyl having 3 to 8 carbon atoms and the alkyl portion is a straight or branched alkyl having 1 to 6 carbon atoms) or cycloalkenylalkyl (wherein the cycloalkenyl portion is a cycloalkenyl having 5 to 8 carbon atoms end the alkyl portion is a straight or branched alkyl having 1 to 6 carbon atoms); each R⁹ independently represents H, straight or branched alkyl having 1 to 6 carbon atoms, alkoxy (wherein the alkyl portion is a straight or branched alkyl having 1 to 6 carbon atoms), alkoxyalkyl (wherein both alkyl portions are straight or branched alkyls having 1 to 6 carbon atoms), aralkyl (wherein the aryl portion is an unsubstituted or substituted phenyl wherein substituted phanyl represents phenyl mono- or di-substituted by alkyl, hydroxy, alkoxy, alkylthio, halo, trifluoromethyl or combinations thereof and the alkyl portion is a straight or branched alkyl having 1 to 6 carbon atoms) or anyl being an unsubstituted or substituted phenyl group wherein substituted phenyl represents phenyl mono-or di-substituted by alkyl, hydroxy, alkoxy, alkylthio, halo, trifluoromethyl or combinations thereof; 35 **P10** represents H. -COR9 or -CON(R9 b: х represents -O-, -S-, or -N(R9)-; m represents 0 or 1; represents an integer of from 1 to 4; represents N or CH; z represents CH2 (if Y does not represent CH) or NR3; and each independently represent integers of from 1 to 3 such that the sum of p plus q is from 1 to 5 and p and q do not both represent 1 when Y is N and Z is NR9. When utilized herein and in the appended claims, the following terms, unless otherwise specified, have 45 the following scope: halo (including the halo of haloalkyt) - represents fluoro, chloro, bromo or iodo; elkyl (including the alkyl portions of cycloalkylalkyl, cycloalkenylalkyl, heteroarylalkyl, alkoxy, alkoxyalkyl - represents straight or branched carbon chains having 1 to 6 carbon atoms; cycloalkyl (including the cycloalkyl portion of cycloalkylalkyl) - represents a saturated carbocylic ring

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50 containing from 3 to 8 carbon atoms; cycloalkenyl (including the cycloalkenyl portion of cycloalkenylalkyl) - represents a carbocyclic ring containing a carbon-carbon double bond and having 5 to 8 carbon atoms;

alkenyl (including the alkenyl portions of aralkenyl) - represents straight or branched carbon chains having at least one carbon-carbon double bond and containing from 2 to 6 carbon atoms;

alkynyl (including the alkynyl portion of aralkynyl) - represents straight or branched carbon chains having at least one carbon-carbon triple bond and containing from 2 to 6 carbon atoms:

aryl (including the aryl moiaty in aralkyl, aralkenyl and aralkynyl) - represents unsubstituted phenyl or substituted phenyl;

substitued phenyl - represents phenyl mono- or di-substituted by alkyl, hydroxy, alkoxy, alkylthio, halo, trifluoromethyl or combinations thereof:

carbonyl oxygen - represents a group = 0:

halpalkyl - represents an alkyl group as defined above containing from 1 to 5 halp groups, (preferably s chloro or fluoro) replacing some or all of the hydrogens thereon depending on the sites of possible halogenation, e.g., CF₃ and, -CH₂CI;

alkanediyl - represents a divalent, streight or branched hydrocarbon chain having from 1 to 6 carbon atoms, the two available bonds being from the same or different carbon atoms thereof, e.g., methylene, ethylene, ethylidene, -CH₂CH₂CH₂-,

heteroaryl (including the heteroaryl portion of heteroarylalkyl) - represents aromatic heterocyclic groups having at least one O, S and/or N Interrupting the carbocyclic structure and having a sufficient number of delocalized of electrons to provide aromatic character, with the aromatic heterocyclic groups preferably containing from 2 to 14 carbon atoms, e.g., 2-, 3- or 4-pyridyl, 2- or 3-furyl, 2- or 3-thienyl, 2-, 4- or 5thiazolyl, 1-, 2- or 4-imidazolyl, 2-, 4-, 5- or 6-pyrimidinyl, 2-or 3-pyrazinyl, 3- or 4-pyridazinyl, 3-, 5- or 6-[1-2-, 4-triazinyl], 2-, 3-, 4-, 5-, 6- or 7-benzofuranyl, 2-, 3-, 4-, 5-, 6- or 7-indolyl, 1-, 3-, 4- or 5-pyrazolyl, 2-, 4- or 5-oxazolyl, with all available substitutable carbon or nitrogen atoms thereof being intended as a possible point of attachment to the benzazepine ring system.

In a preferred embodiment of the invention, R1 represents -XR6, -CHR7R8, cycloalkyl or cycloalkenyl, wherein R⁶ represents -H, phenyl, substituted phenyl, aralkyl, alkyl, haloalkyl or alkoxyalkyl, X represents ·O· or ·S·, R7 represents H or alkyl, and R8 represents cycloalkyl, cycloalkenyl, haloalkyl or alkoxyalkyl. 35 Especially preferred values of R1 are cycloalkyl and cycloalkenyl, in particular cyclohexyl and cyclohexenyl, Where R1 is XR6 preferred values for R6 are alkyl, in particular methyl and ethyl and cycloalkyl, in particular cyclohexyl, and preferred values for X are -O- and -S-.

In a further preferred embodiment of the invention, R1 represents

$$-(CH_2)_m = C = R^9$$

wherein m is 1 and R9 is hydrogen or alkyl. In another further preferred embodiment of the invention R1 is 1-pyrrolyl.

For R2, a preferred value is +H and for R3 a preferred value is -CH3. R4 is preferably halogen, in particular chloro, and R5 is preferably -OH, -O'CO'R9 or -OC(R7) OCOR13 where R9 represents alkyl, alkoxy 50 or alkoxyalkyl, R7 represents hydrogen and R13 represents alkyl.

Preferred compounds of the general formula I include:

8-chloro-5-methoxy-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine-7-ol,

8-chloro-5-ethoxy-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine-7-ol, 8-chloro-5-ethylthio-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine-7-ol,

8-chloro-3-methyl-5-phenoxy-2,3,4,5-tetrahydro-1H-3-benzazepin-7-ol,

8-chloro-3-methyl-5-phenylthio-2,3,4,5-tetrahydro-1H-3-benzazepin-7-ol,

7-chloro-8-dimethylcarbamovi-1-ethoxy-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine,

8-chloro-3-methyl-5-(1-piperidinyl)-2,3,4,5-tetrahydro-1H-3-benzazepine-7-ol,

8-chloro-5-cyclohexyl-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine-7-ol, 8-chloro-5-cyclohexyloxy-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine-7-ol, 8-chloro-5-(N,N-dimethylaminopropyl-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine-7-ol, 8-chloro-5-(2-cyclohexenyl-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine-7-ol,

8-chioro-5-gliyl-3-methyl-2.3,4.5-teirahydro-1H-3-benzazepine-7-ol, 8-chioro-5-(2.2-trithiornethory)-5-methyl-2.3,8-brathydro-1H-3-benzazepine-7-ol, 8-chioro-5-benzylosy-3-methyl-2.3,4-5-teirahydro-1H-3-benzazepine-7-ol, 8-chioro-5-(phenethylosy-3-methyl-2.3,4-5-teirahydro-1H-3-benzazepine-7-ol, 8-chioro-5-(1-pymoly)-3-methyl-2.3,4-5-teirahydro-1H-3-benzazepine-7-ol,

8-chior 2-fudruny-3-methyl-2_3(.5-teitaylvospio(]]H-3-benzaspine-5,5-cyclopmiane], 8-chioro-7-(distoyl-ormylony)-5-y-chioney-3-methy-2_3.4,5-teitaylvor-1H-3-benzaspine, 8-chioro-7-(distoyl-y-chiory)-3-sily-3-methyl-2_3.4,5-teitaylvor-1H-3-benzaspine, 8-chioro-7-(methy-2-castoy)-5-3|hly-3-methyl-2_3.4,5-teitaylvor-1H-3-benzaspine, 8-chioro-7-(actioxy-5-(3-methyl-2-butary)-3-methyl-2_3.4,5-teitaylvor-1H-3-benzaspine, 8-chioro-7-(actioxy-5-(3-methyl-2-butary)-3-methyl-2_3.4,5-teitaylvor-1H-3-benzaspine, 8-chioro-7-(actioxy-6-3-methyl-2-butary)-3-methyl-2_3,5-teitaylvor-1H-3-benzaspine,

and the pharmaceutically acceptable salts of the foregoing.

In another of its aspects, the present invention provides a process for the preparation of a compound of the formula I which process comprises a process selected from the following processes A to E:

A: reduction of a carbonyl compound of the general formula:

30 B: reduction of an ester of the general formula:

$$R^{h}$$
 R^{5a}
 R^{1}
 R^{2}
 R^{1}

C: reduction at the double bond of a salt of the general formula:

$$R^{\frac{4}{5\alpha}} \underbrace{ R^{\frac{1}{2}R^{\frac{3}{2}}} L^{\frac{3}{3}}}_{R^{\frac{1}{2}} R^{\frac{3}{2}} L^{\frac{3}{2}} \oplus$$

D: intramolecular condensation of a compound of the general formula:

.

and with elimination of HD and formation of the azepine ring,

E: reduction at the olefinic double bond of a compound of the general formula:

wherein in the foregoing formulae the dotted line in the azepine ring represents a faculative double bond, R1, R2, R3, R3 and R3 are as defined for formula I, R3 is R3 or COOR12, R3 is R3 es defined for formula I as or is allowy, L3 is an anion, preferably an anion defived from a halo add or a sufficie add, D is a reactive group capable of being eliminated as DH with formation of the azepine ring, and Z1 is R1 or R7, add process being cliently eliminated as DH with formation of the azepine ring, and Z1 is R1 or R7.

(i) removal of any protecting group present at the nitrogen atom,

 alkylation at the nitrogen atom wherein R³ is hydrogen to introduce R³ representing alkyl, allyl or cyclopropyl,

(ii) etherification or thioetherification of R^1 wherein R^1 is -OH and R^2 Is -H to give a corresponding ether or thiol,

(iv) esterification of R5 wherein R5 is -OH,

(v) halogenation of R4 where R4 is -H,

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(vi) hydroxymethylation of R⁴ wherein R⁴ is -H, followed by reduction of the so-introduced hydroxymethyl group to methyl,

and before or after said faculative step or steps, dealkylation of R50 where R50 is alkoxy,

the so-obtained compound of the formula I being isolated in free form or in the form of a pharmaceutically acceptable salt.

The present invention also includes intermediates useful in the preparation of the compounds of formula I, i.e., intermediates of formula II

and the pharmaceutically acceptable salts thereof, wherein:

Q represents H, halo or -OSO₂ R" wherein R" is CH₃, CF₃, phenyl or tolyl;

represents I, Israight or branched alkyl having 1 to 6 carbon atoms, or COOR* wherein R** is straight or branched alkyl having 1 to 6 carbon atoms, any being an unsubstituted or substituted person between the country group wherein abstituted person between the more of discibituted by alkyl, hydroxy, alkory, alkythio, halo, tifluoromethyl or combinations thereof, aralkyl wherein the anyl portion is an unsubstituted or substituted phenyl wherein substituted phenyl wherein substituted with the property represents phenyl mono- or disabstituted by alkyl, hydroxy, alkythio, halo

trifluoromethyl or combinations thereof and the alkyl portion is a straight or branched alkyl having 1 to 6 carbon atoms) or haliaalkyl being a straight or branched alkyl having 1 to 6 carbon atoms substituted with 1 to 5 halo groups;

R¹ represents H, halo, straight or branched allyft having 1 to 6 carbon atoms, haballyf being e 5 straight or branched allyft having 1 to 6 carbon atoms substituted with 1 to 5 hab groups, or allowy fwherein the allyft portion is a straight or branched allyft having 1 to 6 carbon atoms); R¹s spresents - CRP*, - MCP*, - OCRP*, - OCRP* or Maxony (wherein the allyft portion is a straight or branched allyft having 1 to 6 carbon atoms); where R² represents H, or straight or branched allyft having 1 to 6 carbon atoms;

independently represents N, straight or branched alkyl having 1 to 6 carbon atoms, alkowy, wherein the alkyl portion is a straight or branched alkyl having 1 to 6 carbon etoms), alkowyalkyl (wherein both alkyl portions are straight or branched alkyls having 1 to 6 carbon atoms), aralkyl (wherein the anyl portion is an unsubstituted or substituted phenyl represents phenyl mono- or dis-ubstituted by alkyl, hydroxy, alkoys, alkythio, hale, tritiuorimettyl or combinations thereof and the alkyl portion is a straight or branched alkyl having 1 to 6 carbon atoms or anyl being an unsubstituted or substituted phenyl group wherein substituted phenyl represents phenyl mono- or di-substituted by alkyl, hydroxy, alkoys, alkytho, hale, fultiworemethyl or combinations thereof

represents H, -CDR? or -CDOR[*P]; and represents straight or branched skip having 1 to 8 carbon atoms, araily) (wherein the aryl portion is an unsubstituted or substituted phenyl (wherein substituted phenyl represents phenyl mone or disubstituted by skipt, hydrova, skiptilio, haid, filtitoxenetyl or combinations thereol) and the alkyl portion is a straight or branched elkyl having 1 to 8 carbon atomsy or any being an unabstituted or substituted phenyl represents phenyl represents phenyl represents phenyl represents phenyl mone or disubstituted by alkyl, hydroxy, alkoxy, alkythio, haid, brillioxenethy or combinations thereoft;

preferably represents chloro or bromo. A preferred Intermediate is of the formula Ila

The compounds of formula I possess analgesic, anticholinergic, antilaggressive and general tranquitizing properties. The invention therefore includes pharmaceutical compositions comprising a compound of formula I in combination with e pharmaceutically acceptable carrier and further relates to the use of a group of formula I for the preparation of a medicament for treating mental disorders including soychoses, schizopharelar of depression in a manuful, of the footonich of pain of axiety in a manufal.

DETAILED DESCRIPTION OF THE INVENTION

B13

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Certain compounds of the invention, e.g., where R¹ and R² are different, may exist in isomeric forms.

The invention contemplates all such isomers both in pure form and in admixture, including racemic mixtures.

Compounds of formula I can exist in unsolvated as well as solvated forms, including hydrated forms, e.g., hemihydrate. In general, the solvated forms, with pharmaceutically acceptable solvents such as water, ethanol and the like ere equivalent to the unsolvated forms for purposes of this invention.

The compounds of formula I may form pharmacoutically acceptable salts with organic and inorganic acids. Examples of suitable acids for salt formation are hydrochloric, subtric, phosphoric, excite, chitic, maloric, salicytic, malic, fumaric, succinc, accorbic, malec, methanesulforic and other mineral end curboxylic acids well known to those in the art. The salts are prepared by contacting the feet base forms a sufficient amount of the desired acid to produce a salt in the conventional menner. The free base forms sorium hydroide, potassium carbonate, ammonia and sofum biacrobrate. The free base forms their respective salt forms somewhet in certain physical properties, such as solubility in polar solvents, but the salts are otherwise activation to their resceiver free base forms or purposes of the invention.

The compounds of formula I above may be prepared of the methods A-E described below:

A. A compound of formula III may be reacted with a suitable reducing agent to reduce the carbonyl oxygen:

$$R^4$$
 R^5
 $R = R^3$
 $R = R^3$

Suitable reducing agents include BH₂/THF, LiAH₄, NaBH₄/pyridine, NaAH₂(QCH₂CH₂OC₂H₃)₂, etc. The reaction may be performed at any suitable temperature, e.g. from about 0°C to about 120°C, and may be performed in an inert solvent such as THF, either, etc.

The compounds of formula III may be prepared by the processes described below:

III

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For example, a compound of formula IV below may be reacted with a compound of formula V to form a compound of formula VI:

wherein RP is an alkyl group such methyl or ethyl. This reaction may be performed at any suitable temperature, e.g., from about 0° Ct about 50° Cc. Usually an inert solvent such as DMF, Cht-Ch. etc. is employed but the reaction may also be run neat. The reaction is run in the presence of coupling agents or dehydration agents such as dicyclohexylcarbodiimide, N-ethyl-N-(dimethylamino)ethylcarbodiimide.

Alternatively, the compounds of formula VI can be made by reacting the compounds of formula IV with, for example, SOCI₂ or (COCI)₂ to yield the acid chloride of formula IVa

which is then reacted with a compound of formula V. In this reaction, there is no need for a coupling

Compounds of formula IV are either known or may be prepared by techniques conventional in the art. The acotats of formula V are likewise known or easily prepared by conventional techniques. See U.S. patent No. 44,90,369.

The acetal of formula VI is reacted with a strong acid such as CF₃SO₃H, HCl, etc. to produce a compound of formula VII:

VII

III

This reaction may be run neat, i.e., with the acid as the solvent, or in the presence of a solvent such as acetic acid. Any suitable temperature may be employed, e.g., from about 0 ° C to about 50 ° C.

The compounds of formula VII are then reduced to a compound of formula III by employing a suitable hydrogenation agent which will reduce the olefinic bond of formula VII without reducing the carbonyt thereof, 9, 1-8/PC3, 1-8/Pc4, 6, act.

Alternatively, the compounds of formula III may be prepared by a sequence of steps starting with reacting a compound of formula IVb with a compound of formula V to produce a compound of formula VIa, which is then reacted with a strong acid and then a reducing agent to form a compounds of formulas VIII and VIII, as shown below:

wherein R¹² is as defined above. These reactions may be performed under the conditions described above for the respective reaction.

The compound of formula VIII is reacted with a halogenating agent such as SO₂Y₂, e.g., SO₂Cl₂, SO₂Br₂, etc., to produce a compound of formula IX:

This reaction may be run at any suitable temperature and is usually performed in an inert solvent such as CH₂Cl₂, CHCl₃, etc.

The Y group in the compound of formula IX can be hydrolyzed to an OH group which may then be reacted with an appropriate sulfonyl halide or anhydride (such as tolytsulfonyl chloride or methanesulfonyl chloride) to provide other intermediates of formula it above.

The compound of formula IX or the sulfonyl derivatives thereof as described in the preceding paragraph may be neacled with a suitable nucleophile (nu) wherein Y is displaced to prepare a compound of formula X:

$$1X + nu \qquad \qquad R^4 \qquad \qquad N - R^7$$

The nucleophile is the precursor of the group R¹ and can be, for example, an alkanol, primary or secondary amine, a thiol, sodicethylmalonate, cvanide, etc.

If it is desired that R² be other than hydrogen, the compound of formula X may be reacted with a suitable halogenating agent as described above to form a compound of formula XI:

The compound of formula XI is then reacted with a nucleophile (nu) which is the precursor of the group R^2 to displace the group Y and produce a compound of formula III:

$$xt + nu$$
 \longrightarrow $\begin{cases} R^4 \\ R^5 \\ S^1 \\ S^2 \end{cases}$

TT

The reaction conditions for these two steps are as described above in the preceding paragraph. Also, the order of reactions of the nucleophiles may be reversed so that the R^o group is added first and the R^o group second.

As another alternative, the compound of formula VIII may be reacted in an electrophilic substitution reaction with a compound of the formula R*L* wherein L* is a leaving group such as a helogen, e.g., Cl, For I, or a sulfononyloxy group, e.g., tosyloxy, methanesulfonyloxy, etc., to produce a compound of the formula X:

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5 This reaction is run in the presence of a strong base M*1- such as NaH, KH, potassium tertiary butchide, etc. The reaction may be performed at temperatures of from about 0°C to about 100°C may and may be run neat or in an inert solvent such as THF, DMF, etc.

If it is desired that R² be other hydrogen, a compound of formula X may be reacted in another electrophilic substitution reaction with a compound R²L¹ wherein L¹ is as described above to produce a compound of formula III:

$$x \qquad \frac{H^*L^-}{R^2L^1} \qquad \frac{R^4}{R^5} \qquad \frac{1}{R^5} \qquad \frac{1}{R^2} \qquad \frac{1}{R^5} \qquad \frac{$$

This second electrophilic substitution is performed under basically the same conditions as described in the previous paragraph. Again, the order of reaction of the R*L* and R*L* reactants may be reversed so that the R*2 group is added first and the R*1 group second.

The compounds of formula VII above may also be converted directly to a compound of formula I by entrying a stronger reducing agent which will reduce both the olefinic bond and the carbonyl group of the compound of formula VII:

Suitable stronger reducing conditions include, for example, catalytic hydrogenation under elevated temperature and pressure, e.g., with Raney nickel at about 25° to about 100° C and about 20-100 atmospheres. These reductions may be performed in inert solvent such as ethanol.

B. To produce a compound of formula I wherein R3 is CH3, a compound of formula XII may be reduced to give a compound of formula XIII:

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wherein R is an alkyl or aryl group such as methyl, ethyl, phenyl, etc. Any suitable reducing agent may be employed, e.g., LIAHk, etc., in a suitable solvent such as ether, THF, etc. and at a temperature of from 0 °C up to reflux temperature of the reaction mixture.

The compound of formula XII may be prepared by a number of different techniques. For example, a compound of XIV may be reacted with a compound of XV to produce a compound of XVI:

$$\begin{array}{c} R^4 \\ & \\ \text{20} \\ R^5 \end{array} \begin{array}{c} \text{CH}_2\text{CH}_2\text{VHECH}_3 \\ & \text{+ $L^2\text{CH}_2\text{CH}(\text{OR}^{12})_2$} \end{array} \begin{array}{c} R^4 \\ & \\ \text{R}^5 \end{array} \begin{array}{c} \text{CH}_2\text{-CH}_2 \\ & \text{N-CH}_3 \\ & \text{OR}^{12} \\ & \text{OR}^{12} \end{array}$$

XVI

In formula XV L² represents a suitable leaving group such as Cl, Br, I, tosyloxy, methanesulfonyloxy, etc. and R¹² represents alkyl. Any inert solvent such as ether, CH₂Cl₂, CHCl₃, etc. may be employed.

The compound of formula XVI may be cyclized with a strong acid such as HCI, CF;SO₃H, etc. to produce compounds of formulas XVIII and XVIIII (the compounds XVII also being final compounds of the formula I prepared in accordance with Process D of the invention hereinster described in greater detail):

$$\text{XVII} \qquad \frac{\text{strong}}{\text{acid}} \Rightarrow \underset{R}{\overset{R^4}{\underset{OR}{12}}} = \underset{R}{\overset{H}{\underset{OR}{12}}} - \text{CH}_3$$

The compound of formula XVII is separated and reacted with a compound of formula

and then with an oxidizing agent such as ceric ammonium nitrate and sodium bromate to produce a compound of formula XIX:

10 The carbonyl group on the compound of formula XIX may be reduced to a hydroxyl group with a suitable reducing agent, for example, NaBH4, to produce a compound of formula XX:

To convert a compound of formula XX to a compound of formula XXIIa wherein R^1 is $OR^{6\alpha}$, $R^{6\alpha}$ is pheny or naphthly, and R^2 is R, the compound of formula XX is reacted with a compound of formula $R^{6x}OR$ is the presence of disthylazodicarboxylate (DEAD).

$$XX$$
 $\xrightarrow{R^{G_0}OE}$ $\xrightarrow{R^4}$ $N = COOR$ $XIII = OR^{G_0}$

To convert a compound of formula XX to a compound of formula XIIb wherein RP is H, RI is RII and RII is RII other than ORFI, a compound of formula XX is reacted with a sulfourly halde such as tosyl choide (1930) forms a compound of formula XXII is the reacted with a sulfatory halde such as the sulfatory of the RII is goup, e.g., HNRFRII such as methyl amine, an alkand such as methanel, ethand or bencyl adorbol, a third such as methanelhiol, a cyaride such as NACN, etc. to provide a compound of formula XIIb:

XIIb

To convert the compounds of formulas XIIIs and XIIIs to a compound of turnula XIII wherein R is other than H, the reactions described in the preceding two paragraphs are repeated with a nucleophile suitable to provide the desired R'i group. Again, the additions of the R'i and R'i group may be reversed. C. A compound of formula XXIIIs or XXIII are XXIII are additions of the Air a compound R*\formula or R*\formula ', respectively, and then with a suitable hydrogeneting agent such as MBHs, in an intern includin such as a lover alcohol and at a temperature of from 0 *\formula C up to the reflex temperature of the reaction mixture, to provide a compound of formula is:

10

15

wherein L³ represents a suitable leaving group such as an anion derived from a halo acid or suitonic acid, e.g Br, tosyloxy, CI, etc.

The compounds of formula XVIII or XVIII may be prepared by reacting a compound of formula XVIII with a suitable electrophilic agent RPL3 or RPL3, respectively, wherein 13 is as defined above. Suitable electrophilic agents include, for example, benzyl bromide. This reaction may be run in the presence of e base such as potassium carbonate and in the presence in an inert solvent such acetolithile.

By another process, Process E, where it is desired to produce a compound of formula XXIIIa or XXIIIb

the clefinic double-bonds of the compounds of formula XOIIa and XXIIb may be saturated by techniques conventional in the art, for example, by treatment with sodium bondydridd in the presence of a carboxylic acid, e.g., acotic acid in an inert medium at a temperature of from 0°C up to the reflux temporature of the reaction mixture.

D. The compounds of the general formula I may also be prepared by intramolecular condensation of a compound of the general formula

where D is a reactive group capable of being eliminated as DH with formation of the azepine ring. Typically D may be hydroxy, a substituted hydroxy group, in particular altxoxy, a halogen such as anotherine or bromine or a sulfinite call tester such as 7-besty or an O-heavy group. Condensation may suitably be effected by treating the compound of the general formula XVI with a strong acid such as HCI, CFsQxI in an intern medium at a temperature of from D*C up to the reflux temperature of the reaction mixture and then isolating the desired compound of the formula I.

As a finishing step, a compound of formula XXIV may be reacted with e compound of formula XXV to produce a compound of formula it:

XXXV
$$R^{\frac{4}{3}}$$
 $R^{\frac{1}{3}}$ $R^{\frac{1}{2}}$ $R^{\frac{1}{2}}$ $R^{\frac{1}{3}}$ $R^{\frac{4}{3}}$ $R^{\frac{1}{3}}$

25

35

wherein L⁴ Is a leaving group such as Br, tosyloxy, Cl, etc. The compounds of formula XXIV above may be prepared, for example, by treating a compound of formula XII with hydrolyzing agent such as a base, e.g., aqueous or alchoholic KOH or NaOH.

In the above processes A-E, it is sometimes desirable and/or necessary to protect certain R¹, R², R³, R⁴ and R² groups during the reactions. Conventional protecting groups are operable. For example, the groups isted in column 1 of the following table may be protected as indicated in column 2 of the table.

EP 0 285 919 B1

	1. Group to be Protected	2. Protected Group
	-C00B	-cocalkyl, -cocheasyl, -cocphenyl
ı	NE	h-co2alkyl, h-co2pensyl, h-co2cH2ccl3
0	<u> </u>	
5	-он	- o - oce3
5	-не ₂	-\$

Of course, other protecting groups well known in the art may be used. After the reaction or reactions, the protecting groups may be removed by standard procedures.

Also, R¹, R², R³ and R² groups in formula I may be varied by appropriate selection of starting materials from which the compounds are synthesized or by reacting a compound of formula I with a suitable reagent to effect the desired conversion of the substituent to another R¹, R², R³, R³ or R² group.

The utility of the compounds of formula I may be demonstrated by test procedures designed to indicate their anti-psychotic and anti-depressive activity.

CONDITIONED AVOIDANCE SUPPRESSION IN RATS

Clinically active antipsychotic drugs are known to depress discrete trial avoidance behavior at doses that do not returd escape response (Ann. N. Y. Acad. Sci. 68, 740 (1957)). A series of experiments was carried out to assess the ability of the compounds of this invention to suppress the conditioned avoidance response (CAR) in rats.

Materials and Methods

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48 Rats were required to jump onto a platform located 673 inches (17.15 cm) above the grid floor of an experimental chamber in response to a 5-second tone to avoid a 10-second floot shock (08 nm). Each experimental session consisted of 20 such trisls presented at 30-second intervals. A correct CAR is scored whenever the rat jumps onto the platform during the tone (prior to floot shock). An except response is scored when the rat jumps onto the platform during a shock. A response failure is defined as the lack of an o scape response so during the 10-second shock perior during a shock. A response failure is defined as the lack of an oscape response is during the 10-second shock perior during a shock.

Groups of 6-8 rats were trained in two consecutive days (total of 40 trisls). Rats that reached criterion on day 2 (correct CARS on 16 or more of the 20 trisls) were treated with either a test drug or vehicle on day 3. Suppression of CAR was analyzed statistically using Student's 1-test comparing the performances of drug-treated to vehicle-treated rats. The minimal effective does (MED) for each drug is defined as the so (west does lested that significantly (Pc-0.05) reduced avoidance responding.

Results

15

Representative compounds of the invention when tested by the above procedure manifested a doserelated specific blockade of conditioned avoidance response as set forth in Table 1 below:

	Compound					Rat CAR		
	No.	. <u>R⁵</u>	R ¹	$\frac{R^2}{R}$	<u>R³</u>	(mg/kq) sc	(mg/kg) po	
20								
	1	HO-	-осн ₃	-#1	-CH ₃	1	>30	
	2	HO-	-ос ₂ н ₅	-11	-CH ₃	1	>30	
25	3	HO-	-sc ₂ H ₅	-8	-11	<10	-	
	4	HO-	-OPh*	-11	-CH ₃	-	10	
	5	HO-	-SPh*	-11	-CH ₃	>30	>30	
	6	HO	1-piperidinyl	-#	-CH ₃	3	30	
30	7	HO	l-imidazolyl	-#1	-CH ₃	>10	>30	
	8	HO	cyclohexyl	-8	-CH ₃	<u><1</u>	30	
	9	HO	OCH ₂ CF ₃	-#	-CH ₃	1	>30	
35	10	HO	осн ₂ с ₆ н ₅	-11	-CH ₃	3	>30	
	11	HO	O(CH ₂) ₂ Ph	-1 1	-CH ₃	1	>30	
	12	HO	cyclopentyl	-8	-CH ₃	1	>30	
	13	HO	1-pyrroly1	-11	-CH ₃	0.3	>30	
40	14	HO	allyl	-8	-CH ₃	0.1	>30	
	15	HO	-(CH ₂) ₄ -		-CH ₃	1	>30	
	16	Et0002	cyclohexyl	-8	-CH ₃	(3	>30	
45	17	i-PrCO ₂	allyl	-11	-CH ₃	0.3	>30	
	18	MeOCH ₂ CO ₂	allyl	-8	-CH ₃	<0.3	100	
	19	сн ₃ со ₂	3,3-diMe-2- allyl	-1 3	-CH ₃	<1	>30	
	20	POMOO	allyl	-H	-CH ₃	0.1	>30	

[°]Ph = phenyl

COMPETITIVE INHIBITION ASSAY

Many compounds capable of effecting reproducible physiological changes in neural tissues are believed to operate by binding at one or more receptor sites. Compounds which interact strongly with these receptor s sites in in who tests, using homogeneties of the target organ or structure, are expected to exhibit similar properties when administered in who and are, therefore, candidates for confinued study as potential therepowic and/or diagnostic operats.

uner-peace cannot uniquesize agents.

Binding of a compound to a receptor sits, in vitro, is demonstrated by the specificity of binding and the saturability of the available sites. A methodology for characterization of binding and an interpretation of the 10 data are described by Billard et al., Libs Sciences SS, 1885 (1984) in which the binding of the benzazepine (R) (+)9-chloro-2,3,4,5-tetrahydro-5-mothyf-s-phenyl-1H-3-benzazepin-7-ol hemimaleate (SCH 23390) to the dopamine D receptor is characterized.

Materials and Methods

Tritiated SCH 23390 and tritiated spiperone (a potent D-2 ligand) were obtained as described in the Billard et al. reference <u>supre</u> and sensitly diluted in 0.05 M Tris buffer, pH 7.4, as required. A compound of the invention is diluted in 0.05 M Tris buffer, pH 7.4, as required.

20 Tissue Preparation

Mala Sprague-Dawley rats (200 to 250 g) from Charles River Breading Laboratories, Mass. were used to obtain brain tissue. The rats were humanely sacrificed and their brains removed and placed on its. Strietal rissue was excised, pooled, and homogenized (Rinkman Polytron, 10 sec) in 100 volumes (wh) of 26 ice cold 50 mM 1ris buffer, pH 7.4 (at 25 °C). The homogenate was centrifuged at 20,000 xg for 10 min. The resultant pellet was rehomogenized in 17th buffer and centrifyed again. The final pellet was resuspended in 50 mM 1ris buffer pH 7.4 containing 120 mM NaCl, 5 mM KCl, 2 mM CeCl₂, and 1 mM MoCb.

30 Assay

Polypropylene incubation bubes received 100 µL of the individual test compounds at various concentrations dissolved or supposed on 0.05 M Tris, p.17 A containing 4 mg/ml methylocithoss, 100 µL of a solution of 3H-sc)prones in Tris buffer (final reaction mixture concentration =0.3 nM) or 100 µL of a securities of 100 µL of

Results

The inhibition constants (K) determined from the assays for compounds of the invention are as shown in Table 2 below.

TABLE 2

		K* K*			K _j (nM)	
10	R ⁵	R ³	_R ¹	R ²	3 _{H-SCH 23390}	3 _{H-spiperone}
	HO-	-CH ₃	-0CH ₃	-11	54	5600
	HO-	-CH ₃	-ос ₂ н ₅	-8	34	7720
15	HO-	-CII ₃	-SC ₂ H ₅	-1 1	33	2612
	HO-	-8	-sc ₂ H ₅	-H	380	6500
	HO-	-CH ₃	=CHPh°	-	73	705
20	HO-	-CH ₃	-OPh°	-H	83	610
20	HO-	-CH ₃	-SPh*	-H	33	402
	HO-	-сн ₃	1-piperidiny1	-8	. 64	7500
	HO-	-CH ₃	cyclohexyl	−H	10	570
25	HO-	-CH ₃	-(CH ₂) ₃ N(CH ₃) ₂	-H	1100	>100,000
	HO-	-CH ₃	cyclchexyloxy	-11	38	10,100
	HO-	-сн ₃	2-cyclohexenyl	-8	1.1	135
	HO-	-CH ₃	OCH ₂ CF ₃	-11	59	14,900
30	HO-	-CH ₃	OCH ₂ C ₆ H ₅	- H	30	2300
	HO-	-CH ₃	O(CH ₂) ₂ Ph	-11	8	1020
	HO-	-CH ₃	cyclopentyl	-11	21	1538
35	HO-	-CH ₃	1-pyrroly1	-#	11	16,100
	HO-	-CH ₃	allyl	−H	6	170
	HO-	-CH ₃	(CH ₂) ₄	_	19	860
	EtOCO ₂	-CH ₃	cyclchexyl	-11	133	3334
40	i-PrOO ₂	-CH ₃	allyl	-1 1	84	3447
	MEOCH ₂ CO ₂	-сн ₃	allyl	-11	10.3	566
	сн ₃ со ₂	-сн ₃	3,3-diMe-2- ally1	-#1	17	955
45	PCM**	-сн ₃	allyl	- H	240	2620

[°]Ph = phenyl

The comparatively small K₁ values of these compounds in the competitive binding assay with SCH 52 3339 indicate that the compounds of formula I bind strongly to the D-1 receptor site. The relatively high K₁ values for the D-2 site, for which spiperone is highly selective, indicates that the compounds are not specifically bound to that receptor site.

The antidepressive method of the invention is identified, for example, by test procedures which measure a compound's effect on tetrabenazine (TBZ)-induced ptosis in mice or which measure a compound's effect on mulridule activity in rate as discussed below.

5 ANTIDEPRESSANT POTENTIAL

EFFECTS ON TETRABENAZINE (TBZ)-INDUCED PTOSIS IN MICE

Clinically active antidepressant drugs are known to block TBZ-induced ptosls in mice (Psychosomatic Medicine, Nodine and Moyer, Eds., Lea and Febiger, Philadelphia, 1982, pp 683-90). Activity in this test is used to predict anti-depressant activity in man.

Methods and Materials

Groups of 5 mice are administered test drugs followed 30 minutes later by ip injection of tetrabenazine, 30 mg/kg. Thirty minutes later, the degree of priosis is evaluated. Percent blockade of each treated group is used to determine ED₀'s, defined as that dose which prevents ptosis in 50% of mice. ED₀'s and 95% confidence limits are calculated by probit analysis:

20 EFFECTS ON MURICIDAL BEHAVIOR IN RATS

Blockade of muricidal (mouse-killing) behavior in rats is used as a measure of evaluating the antidepressant activity of drugs (Int. J. Neuro-pharmacol., 5, 405-11 (1988)).

25 Methods and Materials

Groups of 5 rats are administered test drug intraperitonially and are tested 30 and 60 minutes later for presence or munificial behavior. Percent blockade of each treated group using data obtained at both these time points is calculated and dose-response data are used to determine each Ebp.: Ebp. is defined as that 3 dose which blocks muricide behavior in 50% of treated rats and is calculated using protit analysis.

The analgesic effect of the compounds of formula I and the method for providing analgesia may be exemplified by the Acetic Acid Writing Test in Mice described below.

ACETIC ACID WRITHING TEST IN MICE

The blockade of writhing induced by the intraperitoneal injection of acetic acid is an established experimental animal model for the screening of antinociceptive drugs (drugs which prevent the appreciation or transmission of pain sensations). See Hendershot et al., J. Pharmacol. Exp. Therap. 125:237, (1999) and Koster et al., Fed. Proc. 18:412 (1999).

METHODS AND MATERIALS

Compounds to be tested are dissolved or suspended in aqueous 0.4% methylcellulose vehicle. For oral administration, dosages are prepared for delivery of the selected weight of compound in e total volume of < 20 mg/kg of body weight. For subcutaneous or intraperitioneal administration, dosages are prepared for delivery of the selected weight of compound in a volume of 10 ml/kg of body weight.

The test procedure is that described by Hendershot et al., sugra, except that assic acid is substituted for phenyiquinnoe. Groups of the metic CF insic (20-26 g.) are dosed only with test drug and injected 15 minutes later with 0.6% acueous acetic acid (10 mg/kg). The mice are placed in a large observation beaker so the number of writhes for each animal is counted during a 10 minute interval starting 3 minutes etter injection of eactic acid. A writhe is defined as a sequence of arching of the back, pelvic rotation and hindlimb extension. Initial screening is performed using a dosage of 30 mg/kg. If this dose effords 50% or greater reduction in the number of writhes compand to the control, the animal is considered to be protected, e dose response curve is developed using a logarithmic sequence of lower doses and an ED₂ is determined by interpolation.

Regarding toxicity, the compounds of this invention are non-toxic at the therapeutic dose.

For preparing pharmaceutical compositions from the compounds of formula t, inert, pharmaceutically acceptable carriers are edmixed with the active compounds. The pharmaceutically acceptable carriers mey

be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachest and suppositories. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, briders or tablet disintegrating agents; it may also be an encapsulating material. In powders, the carrier is finely divided solid which is in administra with 5 the finely divided active compound. In the tablet, the active compound is mixed with a carrier having the necessary binding preparates in suitable proportions and compacted in the shape and size desired. The powders and labels typically contain from 5 to about 70% of the active ingredient dependent upon the powders and labels typically contain from 5 to about 70% of the active ingredient dependent upon the powders and labels typically solid carriers are magnesium cachonist, magnesium stranta, late, sugar, to lactose, poctin, doxtrin, starch, gelatin, tragacanth, methytebulises, sodium carbonymethytebulises, a low melting wax, cocco butter and other materials typically used in the pharmaceutical industries. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as carrier, providing a capsule in which the active component (with or which other carrier) is surrounded by a carrier, which is thus in association with it. Similarly, caches are included. Tables, powders, caches and appearance and the series of the series of the proper and the series of the capsules can be used as solid closepters causalists for oral administration.

For preparing suppositories, a low melling was such as a mixture of tatly acid glycerides or occosbutter is first melted and the active Ingredient is dispersed homogeneously therein as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool end thereby

20 Liquid form preparations include solutions, suspensions end emulsions. As an example may be mentioned water or vates-proprise glycol solutions for praenteral rejection. Liquid preparations can also be formulated in solution in equeous polyethylene glycol solution. Aqueous solutions suitable for oral use can be prepared by adding the active component in water and adding suitable colorants. Kennys, stabilizing, severations, solutilizing and thickening agents se desired. Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with Ascous materials. La, natural or synthetic gums, resins, methylcallulose, sodium carboxymethylcallulose and other well-known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, so auspensions and emulsions. These particular solid from preparations are most conveniently provided in unit does form and as such, are used to provide a single liquid dosage unit. Alternatively, sufficient solid may be provided so that efter conversion to liquid form, multiple Individual liquid doses may be obtained by measuring prodetermined volumes of the liquid form preparation as with a syringe, teaspoon or other volumetric container. The solid form preparation as mineral to a form any contain, in as eddition to the active material, flavorants, colorants, stabilizers, buffers, artificial and natural sweetners, dispersants, trikeners, solubilizing agents and the like. The solvent uitized for preparation pluciful or preparation may be water, isotonic aqueous sait solutions, ethanol, glycerine, propylene glycol and the like, as well as michures shrenof. The solvent uitized with be chosen with regard to the roots of administration.

The invention also contemplates alternative delivery systems including, but not necessarily limited to, transdermal delivery. The transdermal compositions can take the form of creams, tolions and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

Preferably, the pharmaceutical preparation is in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active components. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation such as packeted tablets, capsules and powders in visit or amputes. The unit dosage form can also be a capsule, cachet or tablet itself, or imay be the appropriate number of any of these in a packaged form.

The quantity of active compound in a unit dose preparation may be varied or adjusted from 1 mg to 100 mg according to the particular explication and the potency of the active ingredient end the intended treatment. A dose of about 0.02 to about 2.0 mg/kg, preferably about 0.02 to about 0.2 mg/kg, may be employed and may be divided over 1 to 3 administrations per day. The composition may, it desired, also contain other theraportic agents.

The desages may be varied depending on the requirement of the patient, the severity of the condition being treating and the particular compound being employed. Determination of the proper dosage for a particular situation is within the skill of those in the medical art. For convenience, the total daily desage may be divided and administered in portions throughout the day or by means providing continuous delivery.

The invention disclosed herein is exemplified by the following examples which should not be construed to limit the scope of the disclosure. Alternative mechanistic pathways and analogous structures within the scope of applicants' invention may be apparent to those skilled in the art.

5 PREPARATIVE EXAMPLE 1

20 A mixture of 30.0 g of the compound of formula A above, 32.8 g of bromosoetaldehyde diethylacetal, 50 g of anitymous KpC0, and 150 ml day dimethylarmanide (DMP) were stiered and headed under introgen to 120 °C. After two hours, the solution was filtered, and the filtrate poured into water. The mixture was extracted twice with 200 ml of either, the combined bether layers washed with brins, diefed and concentration to a oil (38.4 g). This layer chromotography showed the compound of formula B above as the only major product, R = 0.73 developed with ORDs/CHQ-DMINHOH-10000400.

EXAMPLE 1

Step A

The compound of formula 8 (3.4 q) required as described in Preparative Example 1 was mixed at ichboth temperature with 10 ml of methanesultoric acid, and the resulting solution then heated to 70 °C. After 45 two hours, the resulting mixture was pound into acid sexcess salurated NaHCOs, solution. The mixture was extracted with ether. The extracts were washed with brine, dried and concentrated to an oil (2.7 g). The product was dissolved in other and treated with a slight excess of exheral HCI. A yellow gum respurated and crystallized. Filtration of the solid and recrystallization from 2-butanone gave the compound of formula C above as a hydrochholide salt, pp. 158-197 °C.

Step B

5

10

$$C + Masc_2 H_5$$

$$C1$$

$$H_0 - CH_3$$

$$C2$$

15 The compound of formula C (750 mg) prepared in Example 1A in 20 ml of dimethyllomanide was added droprise to a solution prepared from 60% sodium hydride in minest all (480 mg) and ethaneshille (0.9 ml) in 20 ml of dimethyllomanide. The resulting mixture was heated at 130°C for ten hours, poured into wate, and extracted with either. The appeace layer was rebasefied with solid Nalt-Co, and the pre-pricipated oil extracted aspain with either. The appeace layer was rebasefied with solid Nalt-Co, and the pre-pricipated oil extracted on with eithyl accelete. The extract was washed with brine, dired over anhydrous MigSOs, and concentrated to an oil, which was dissolved in either and treated with eitherael NCI. The precipitated extra was separated by decantation, and recrystallized from acetone to give the compound of formula D above as a hydrochloride salt, m.o. 25°2.520°C.

By employing basically the same process as described in Example 1, using an appropriate as dimethylacetal of bromoacetaldehyde, the following 5-alkoxybenzazepine-7-ol was prepared:

PREPARATIVE EXAMPLE 2

Step A

A solution of the compound of formula C above (19.5 g) in 250 ml of benzene was tosted at mflux with 20.7 ml of bryit-chroformate. The resulting solution was heated for three hours at reflux, the sehrent their removed in vacuo, and the residue partitioned between other and 5% HCI. The other layer was superated, washed with brine, dired and concentrated to a dark gum, which was dissolved in petroleum either, treated swith Dacro and Florist and filtered. The filtrate was concentrated to a yellow oil (16.9 g). Thin layer chromotography showed the compound of formula E above as a single spot, R₁ = 0.46 (fex-anesthylacetate-21).

Step B

The compound of formula E above (16.9 g) was dissolved in 175 ml of acetonitrile and treated with a solution of 8.45 g of sodium bromate and 548 mg of ceric ammonium nitrate in 75 ml of water. The twophase mixture was stirred at relitu for 24 hours.

The cooled mixture was diluted with 250 ml of water and extracted twice with 250 ml of other. The ether phase was washed with brine, dried and concentrated to a gum. Trituration with ether/petroleum ether aftorded the compound of formula F as prisms (6,0 g), m.p. 134-135* C.

EXAMPLE 2

10

Step A

35 The compound of formula F above (1.0 g) (prepared as described in Preparative Example 28 and wherein R1 topheth with R2 represent carbonly was supended in 20 m of absolute retained and steaded with 140 mg of socium borohydride, portionness, with sisting. The mixture was warmed to 40° C and stimed for 20 minutes, siter which 10 m of 5% HCI and about 10 g of the overe added. After stringing another 30 minutes, the solid product was filtered, and dried to give 930 mg of the compound of formula G above, m.p. ed 18-1144 °C.

Step B

A solution of 0.45 p of the compound of homula G above in 10 ml of ry dimethyllomanifide was added in 10 ml of dimethylomanifide. The resulting solution was heathed at 125°C owenight. It was then pound into water, and extracted with other. The auguous phase was acidified to pH 1 and rebasilide with solid NaHCOs. The oily product was extracted with 64th yallotate and the solution evaporated to give the

compound of formula H above as a crude product (0.4 g). This compound was converted to its hydrochloride by treatment of an ethereal solution with a slight excess of ethereal HCI. The resulting salt was filtered and dried in vacuo to produce a within amorphous solid.

5 EXAMPLE 3

$$E + CE_3 I$$
 $\frac{DMF}{(C_2 E_5)_3 M}$ $C1$ $N - CE_3$

The compound of formula H (0.4 g), prepared as described in Example 2, was dissolved in 5 ml of directly/commission, 2 ml of triefly/amine added, followed by (0.93) and in orthopticidis. The resulting mixture was allowed to stand at room temperature overright, after which it was poured into water. The or mixture was actorated with only acetale, directly and concentrated to an oil. This method [250 mg) was chromotographed on 25 g Morck silica get 60-G, okuling with CHCip/CHy0H NHv0H - 1000593. A component, TTC homogeneous (fig. ~ 0.69), same solvent system), was obtained (156 mg) which was dissolved in other and treated with an ethereal solution of 45 mg maleic each. The precipitated solid was fittered and dired in vecus to give 88 mg of the component formula above as the mislates sait.

Analytically calculated for C₁₃H₁₈NOSCI.C₄H₄O₄: C 52.64; H 5.72; N 3.61. Found: C, 52.14; H, 5.60; N, 3.46. FAB mass spectrum m/e + 1 = 272.

PREPARATIVE EXAMPLE 4

(wherein Phophenyl)

Triphenylphosphine (0.57 g) and phenol (0.21 g) were added to a solution of the compound of formula (0.69 g), prepared as described in Example 2.4, to 30 mt of brazzene. To this solution was then added and their solution of discopropylazodicarboxylate (0.433 mt) in 10 mt benzene over five minutes. The resulting another solution of discopropylazodicarboxylate (0.433 mt) in 10 mt benzene over five minutes. The resulting instruction and solution of the compound of town of the compound of townsia Kabova as a yellow oil.

When the compound of formula K abova as a yellow oil.

EXAMPLE 4

Step A

18 The compound of formula K above (450 mg) in 20 ml of ether was added to a suspension of lithium sulminum hydride (53 mg) in 20 ml of ether. The misture was allowed to sirt at prometime preparative for the hours, and was then decomposed by treatment with cold 10% NaOH solution until all solids dissolved and the phases separated. The squeues phase was extracted with eithyl acetale and the combined organic layor washed with brine, dried and concentrated to an oil (350 mg) which solidified on drying overnight in 20 vacuo to provide the compound of formula L above.

Step B

A solution of the compound of formula L above (350 mg) in 10 ml of dimethyllormamide was added a drophrise to a solution of sodium thioethoxide prepared from 132 mg 50% Ne14/mineral oil dispersion and 0.405 ml oil ethanethiol in 5 ml oil dimethyllormamide. The resulting mixture was stimed for three hours at 100°C under a nitrogene atmosphere. Solvent was removed in vacuo, and the residue partitioned between water and ether to provide the compound of formula M above, mp. 166-189 °C.

By employing in Preparative Example 4 the substituted phenol listed in the first column of Table 3 oblow in place oil phenol and basically the same processes as described in Preparative Example 4 and Example 4 above, the products listed in the second column of Table 3 may also be prepared.

TABLE 3

Product

Phenol R¹ =

So
$$C_1$$
 C_1 C_1

So C_1 C_2

So C_1 C_2

So C_1 C_2

So C_2 C_3

So C_4 C_5

PREPARATIVE EXAMPLE 5

To a stired solution of tri-hully(phosphine (pl.485 g. 24 mmole in benzene (10 ml) was added solid N-(phenylthio)succinimide (175 mg. 24 mmole) in one portion. The resulting solution was stirred at ambient is temperature for five minutes, then the compound of formula C (554 mg. 1.8 mmole), prepared as described in Example 2A was added all at once. The minuter was stirred at ambient for about 12 hours. An additional 0.2 ml of tri-hully(hosphine was added and stirred in an additional 2 hours.

The resulting mixture was concentrated to dyness and water and ethan/hoxane 1:1 were added. The organic phase was washed with brine, dried and concentrated to a gum, 0.8 g. The gum was chromotogzor raphed on about 8.0 g Morck silica gel G, eluting with hoxane, then hoxane/bityl acetate 1:4 to yield 0.8 g of the compound of formula N above, which was characterized by NMR and TLC. (R₁ = 0.3 in ethyl acotate/hexane 1.3)

EXAMPLE 5

Step A

The chromatographed compound of brmule N above from Preparative Example 5 (0.55 g. 1.4 mmole) in 20 mt other was added to an Ice-cooled slury of 70 mg (1.8 mmole) lithium aluminum hydrids in 20 mt of other. The cloudy solution was stirred at ambient temperature for about 50 hours. An additional 40 mg of 40 LIAIK, in other was added. After 30 minutes TLC showed complete reaction. Cold 10% NoRIH was added until all solids disasohed. The aquious layer was expented and extracted with ethyl acetals. The combined organic layers were washed with brine, dried and concentrated to provide the compound of formula P above as a gum. 0.47 g.

Step B

The compound of formula P above (0.42 g, 1.25 mmole) was added in 5 ml of DMF to a solution of south thiosthoxide (prepared from 100 mg (2.5 mmole) NaH 60% in oil dispersion and 0.185 ml (2.5 mmole) otherwistic in 10 ml DMF) and the clear solution stirred at 100-110°C for about 32 hours. An

additional 2.5 mmole of sodium thioathoxide (prepared as above) was added and the reaction mixture heated an additional 3 hours at which time TLC showed virtually complete reaction.

The mixture was poured into water and extracted with horane. The basic aqueous solution was acidified to pH 1 with 5% HCl and re-extracted with hoxane. The acid phase was basified with solid NaHCO, and se extracted with ethyl acreate to yield 400 mg of oily product. Upon standing, the material crystallized. The solid was recrystallized from ether/petroleum ether to yield 170 mg of the compound of formula Q above, mp. 1584672.

PREPARATIVE EXAMPLE 6

Step A

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BS ml of thionyl chloride was added dropvise to a solution of 64.0 g of the acid of formula R above in 1 oil ofly dichloromethane with stirring. The mixture was stirred at room temperature for 3 hours longer and then heated on a steam bath under gentle refluxing for two hours. The low boiling material (solvent and excess SOCs) was distilled off at about 50°C under vacuum. The residue was dried under vacuum at room temperature for 2 hours longer.

The concentrated solid chloride produced was dissolved in 120 ml of CH₂Cb, and then added dropwise to a stirring solution of 50 ml of hrealty-tamicostatablevide dimentylacetal and 80 ml of theirly-tamics (50% excess) in 350 ml of methylene chloride for 1.5 hours at 20-25°C with occassional cooling. The mixture was stirred at room temperature for one hour longer. The reaction mixture was extracted twice with 500 ml of water, dried over MgSQs, filtered and then roto-exported down to dryness to provide about 100 or of the commount of formula's above as a viscous syrup.

Step B .

$$S \longrightarrow CH_3O \longrightarrow N - CH_3$$

The viscous syup was added in small portions to 500 nnl of concentrated NOI (previously chilled in an ice bath) with cooling and stirring (see bath). This was turther diluted with 500 ml of acetic acid. The mixture so was stirred at room temperature overnight. The reaction mixture was poured into 8 liters of ice and H₂O with stirring over 30 minutes. A gummy solid was filtered off and washed with water. The filtrate was extracted with one liter of 10-10-2 and roteverparehal down to dynams. The residue of the roteverparehal of the water of the community of the

Step C

68.0 g of the material of formula T from Preparative Example 68 above were dissolved in 600 ml of ethanol which was then divided into two equal portions and each portion was reduced with H₂ over 2.5 g of the control of the contro

After removing the catalyst, the filtrates of both runs were combined, checked with TLC and is rotoexparented down to dryness. The residue was stirred with 150 m of cold ethyl acetate with seeding. The solution was chilled in an ico bath, filtered and the solid was washed with cold ethyl acetate to provide about 28.0 g of the compound of formula. U. 24.0 g of this material and 12.0 g from another batch were combined and discoved in 100 mil of boiling ethyl acetate. The mixture was cooled in a freezer and filtered, and the solid was washed with cold ethyl acetate. The solid was dried at room temperature for one hour to a provide 28.00 or of the compound of formula U. no. 104-105* C.

Step D

To a solution of the compound of formula U above in 300 ml of CH₂Cl₂ was added a solution of 15 ml of CH₂Cl₃ in 35 ml of CH₂Cl₄ in a 5 ml of chief in a considerable of 2 12 hours longer and poured into 500 ml of los water with stirring. The organic layer was 3 died over MgSO₄, filtered and then rotervaporated down to dyness. The residue crystallized out partially. The mixture was then triturated with 40 ml of cold othyl cacetate to provide 13.90 g of the compound of formula W, m.p. 162-164 °C.

The filtrate was kept in a freezer overnight and then filtered to provide an additional 1.20 g of the compound of formula W of lesser purity.

To a stirred suspension of 1.20 g of the compound of formula W above and 2.0 g of K;COs, in 10 m ld of DMF was added in one portion 430 mg of piperfeline. The mixture was stirred at room temperature and pound into 700 m ld of water with stirring. A gummy solid was filtered off. This wet solid was dissolved in 50 m ld CH;COs and extracted with 50 m ld 14;O. The organic layer was separated, dried over K;COs, filtered and then closex-portable down to dyness. The residue was recyptalized from accelerating (10 m) to

provide 700 mg of the compound of formula Z, m.p. 139-141 °C.

EXAMPLE 6

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Step A

A solution of 2.95 g of the compound of formula 2, prepared as described in Proparative Example 6E, 20 in 20 ml of 11% end 40 ml of diozone in THE (10.8M) was heated on a stame that funder femilus for 18 hours. The mixture was distilled to dryness. The residue was treated cauliously with 25 ml of 4 N HCI and then heated on a steam bath with stirring for 30 minutes. The mixture was chilled and diluted with 30 ml of water, made batic with N40H and then extracted wide with 50 ml of other. The other layers were 50 ml of 40 ml of 50 ml of 50

Step B

A80 mg of the compound of formula Aa above in 10 ml of aqueous 49%. Hith was heated at 130°C with stirring for 6.12 hours. The minuture was powerf limin 100 ml or lot wester and the pit aliquisted to about 8 with NaHCOs. The minuture was extracted twice with 40 ml of CH₂Cb. The diried combined extracts were introvaporated beaving 280 mg of crange colored gum-the material which was purified through 30 mg of 45° TLC grade sitics get, etuting with CH₂Cb/CcH₂Cb/HHACH (S0XH). The residue from rotovaporation of the fractions containing the desired component was desired of 30 ml of either and allowed the oxportuse slowly to about 5 ml. The solid produced was filtered off, dried at 80°C for 5 hours to provide 75 mg of the compound of formula AB above, np. 155-15°C.

By employing the Reactants listed in the first column of Table 4 below in place of piperdine in By employing the Reactants size of piperdine in By employing the Reactants is the same procedure as set forth in Proparative Example By Earn Example 6 above, the compounds listed in the second column of Table 4 may also be synthesized.

TABLE 4

PREPARATIVE EXAMPLE 7

Step A

A mixture of 1.40 g of the compound of formula W, prepared as described in Preparative Example 6D, 4.0 g of NaHCO $_2$ and 1.75 g of sodium dithionite in 20 ml each of DMF and H_2O was stirred at room

temperature for 1 1/2 hours. 200 ml of water were added with stirring. The mixture was filtered and the solid separated was washed with water to provide about 1.09 g of solid, which was recrystallized from acetonitrile to provide a small amount of the desired compound of formula AC, m.p. 117-118°C. The filtrate from the acetonitrile recrystallization provided 950 mg of less oure compound of formula AC.

Under N₂, NaH (676 mg, 60% oil dispersion) was added to a solution of the compound of formula AC (2.5 g) in 150 ml of THFOMF (10.1) at norm temperature. A solution of cyclohacy thormide (1.5 cg) in THFOMF (10 cg) was added via dropping furmel to the above mixture. The mixture was heated on an oil bath at 80 °C. After 2 hours the reaction was complets. Solvent was removed on a robeoxpapertor 41 of C (cump associated) and the residue was diluted rapidly with 200 cc of ice water. The resulting mixture was extracted with 200 ml of C1-(cg) and the C1-(cg) keyer was separated and died over MgOS. Robeoxpapert ton of the C1+(cg) keyer gave 3 g of amorphous solid which was chromatographed on Klassiqel 800 using entry accessible shareare (450%) as the eluant to give about 1.54 g of the product of formula AC.

EXAMPLE 7

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The compound of formula AD (153 B), prepared as described in Preparative Example 78, dry THF 60 cc) and diborage (16 cc) of all Nosbullon IT-HIP year reflaused for 2 Nz. The reaction institure was cooled to room temperature and 5 cc of H₂O was added carefully. Solvent was removed on a rotoevaporator at about 30°C. Ethanof (100 cc) and 25 cc of HH NF olivers added to the residue, and this institure refluxed on 4s astern bath for 1 12 hours. Ethanol was removed on a notevaporator at 50-60°C, and the remaining acquous portion was distude with 100 not of low when. The mixture was basisfied with 10% NoOH soldron to a PH of about 8 and extracted twice with 100 cc portions of CH2-Cg. The combined extracts were dried over MgSO, and experted to give 128 g of the compound of Inormula & Babove as an oil.

A solution of the cycloharyl compound of formula AE above (1.2 g) in 6 ml of dimethylorimamide (DMF) was added to a solution of sofum thisothoxide in 6 ml of DMF prepared from 757 mg of 60% 15 sociam hydride in mineral oil and 1.4 ml of ethaneshiol. The resulting mixture was heated at 120° C on an oil bath for 4 hrs, cooled, disluted with 100 ml of it-eventer, and washed with 50 ml of hasnes. 5% HOI was added to the separated acqueus layer to adjust the pH to 7.58. The mixture was extracted twice with 200 ml portions of CH-Cl₂Ci, and the combined extracts were divide over MgOQ, filtered, and evaporated to give an oil which was dried in high vacuum. The oil partially crystalized and was recrystalized from ether-period the combined of the combined services of the combined services. The combined services have been described to the combined services and the combined services are described and was recrystalized from ether-period combined services.

By employing the reactant listed in the first column of Table 5 below in place of cyclohexyl bromide in Preparative Example 7B above and by employing basically the same basic procedures as set forth in Preparative Example 7B and Example 7, the compounds listed in the second column of Table 5 were also synthesized.

TABLE 5

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Roactost

By amploying the CH₂ = CH-CO₂CH₃ in place of cyclohaxyl bromide in the procedure of Preparative So Example 78 and by employing basically the same procedures as described in Preparative Example 78 and Example 7, the compound AS shown below may also be prepared:

AG

15 PREPARATIVE EXAMPLE 8

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A solution of sodium ethodde in 30 ml of absolute ethanol was prepared by using 253 mg of sodium, the compound of formats W 2.75 g), prepared as described in Preparative Example SI, was added to the solution, and the reaction mixture was heated under reflax for 3 hours. The mixture was rotovaporated or down to drynass. The residue was treated with SI on leach of H₂CO and CH₂CC, The CH₂CC portion was dried with MgSOs, and concentrated to dryness to provide 250 g of a solid residue which was recrystalized from 15 ml of actionthiritie to give about 780 mg of the compound of formula AH above, mp. 109-108 °C.

EXAMPLE 8

A solution of 775 mg of the compound of formula AI, prepared as described in Preparative Example 8, in 20 ml of THF was added to 15 ml of diborane/THF (1,08 M) with stirring. The mixture was heated under reflux for 5 1/2 hours longer and then distilled to dryness. The residue was treated with 15 ml of 4 N H Cl of the 10 ml of 1 ml o

Step B

AI
$$\frac{\text{NaSC}_2^{\text{H}}_5}{\text{BO}}$$
 $\frac{\text{C1}}{\text{DO}_2^{\text{H}}_5}$ N^- CH₃

NaSG-ht, was prepared in DMF with 1.50 g of NaH (80% in oil) and 3.0 m of enhansition in 3.0 m of DMF. To 4 got this contion was added a solution of 1.20 g of the compound of formula A labore in 2 m of DMF. The mixture was heated on an oil bath at 130-140 °C for 4 hours and then chilled to room temperature and poured lint 1.50 m of a vater. They have adjusted to about 8 with droppies addition of 15 acut acid. The mixture was extracted horizon with 1.50 m of 1.04-Cb. The CH-Cb, layers were dried over Ag50, filtering, then rollowage pointed drown to about 4.5 m and them distilled down to dryness at 10 mm at 59 °C. The mixture was purified through a column of 50 g of TLC grade slice gel bulling with 59 °C. The mixture was provided through a column of 50 g of TLC grade slice gel bulling with 70 °C. The mixture was provided through a column of 50 g of TLC grade slice gel bulling with 70 °C. The mixture was provided through a column of 50 g of TLC grade slice gel bulling with 8 slight access of dry HCl. The resulting salt was filtered and dried in vacuo to provide the HCl salt, no. 235-238 °C (decomposed).

EXAMPLE 9

To a suspension of 0.8 g (2.7 mmole) of the hydrochloride of the compound of formula AJ, prepared as described in Example 8, in 20 ml dry dimethoxyethane was added 210 mg of NaH (60% in oil dispersion) (5.5 mmole) in portions with stifring. After evolution of gas had stopped (about 10 minutes) a soution of a dimethylcarbamyl chloride (0.290 g, 0.248 ml, 2.7 mmole) in 10 ml dimethoxyethane was added and the makeur was strifted at ambinet incompratuse overwinds and then heated to 50 °C for 3 hours.

The reaction mixture was filtered (obtained 0.32 g solid, theoretical NaCl) and evaporated to near dryness. Ether and dilute NaOH were added. The phases were separated. The other phase was washed with brine, dried over MgSO₁, decolorized (Darco and Florist) and concentrated to a gum, 0.9 g, which was the compound of formula AK as confirmed by NMR.

This gummy material (0.9 g) of formula AK above from Example 9 was dissolved in either and treated with a slight excess of eitheral HCI and then filtered. The hygroscopic solid separated was redissolved immediately in about 20 ml of acelentifile, diluted with about 100 ml ether, cooled and filtered to provide 520 m of the desired compound of formula AK above as the hydrochloride, m.p. 199-202 °C.

PREPARATIVE EXAMPLE 10

35 Sodium hydridid (1.18 g. 60% oil dispersion) was added under nitrogen to a solution of the compound of the formula AC (3.5 g. prepared as described in Preparative Example 73) in SS and 17FE/DMF ((10.1) was then added via a syringe and the motiture heated at \$0.0 C to (3.5 hours and then at \$5° for 1 hour. The solvent was removed on a rottowaporative at 40° C and 200 cc of lox water rapidly added to the residue. The resulting mixture was was extracted with he oil \$50 c c portion of CH-(5.6) and the combined orbatract washed with a \$50 c c portion of water and then diried over MgSO. Rottowaporation of the CH-(5), extract gave 3.5 g of an oil. Recrystallization from a midful actabationam mixture (4.90%) owe 2.8 o of the product of the Formula AL.

EXAMPLE 10

EXAMPLE 10

Step A AL
$$\xrightarrow{\text{LiAlH}_4}$$
 C1 $\xrightarrow{\text{N-CH}}$ CH₃0 AM

40 A solution of the compound AL (2.8 g), prepared as described in Preparative Example 10, in THF (30 cc) was added at room temperature to a suspension of LiARH, (1.1 g) in THF (50 cc). After 1 hour the resiction was complete as Indicated by this layer chromatography. To the resultant reaction mixture was added 1.1 cc of water, 1.1 cc of 15% NoRH solution and then 3.3 cc of water. The precipitate was filtered off, the THF removed on a rotowaperator and then 200 cc of water added to the residue. The mixture was 45 then extracted with two 150 cc portions of CH₂CH₂, the combined extract washed with a 75 cc portion of water and then dried over MgOs. Rotowaperation of the dried CH₂CH₂ layer grow an oil which was chromatographed on a sitica column using a 1:1 mixture of athyl sociate and hexare as eluent to give the desired product AM as an oil (152 cl).

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Step B

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$$\stackrel{\text{NaSC}_2H_5}{\longrightarrow} \stackrel{\text{Cl}}{\longmapsto} \stackrel{\text{N-CH}_3}{\longmapsto}$$

NaSCyt, was prepared by adding batchwise 0.89 g of NaH (60% oil dispersion) to an ice-cold solution of 1.6 cc of leatherfloir 20 cc or 0.0MF. The reaction mixture was allowed to starf for 15 mitutes and then a solution of 1.45 g of the compound of the formula AM in 30 cc of DMF was syringed into the mixture. The resulting reaction mixture was netted on an oil bata at 120° Cer 2 hours, cooled to come temperature and then 400 cc of vater added. The pH of the product mixture was adjusted to 1 with N HySOs, the mixture extracted once with 150 cc of cliently either and then basified with solid NaH/COs to give a pH of 8. The mixture was extracted with two 150 cc portions of eithyl acotate and the combined extract then dried over MySOs, and then evaporated to give and (840 mg). The oil was chromatographed on a silical column using so 11: eithyl acotatehexane as eluant to give 440 mg of product which was recrystallized from an ethyl acetatehexane mixture to give 300 mg of the desired product AM (nr., 1411-145° C).

Using the procedures described in the foregoing Examples, the compounds of the general formula I set forth In the following Table 6 may be prepared.

TABLE 6

10	Compound	_		_	_	
	No.	<u>R⁵</u>	<u>R</u> 1	R ²	R ³	m.p. °C
15	1	HO-	=CHC ₆ H	l ₅	-CH ₃	190-193
	2	HO-	-∞ ₆ H ₅	-#	-сн ₃	180-182 (maleate)
	3	HO-	l-imidazolyl	-11	-CH ₃	194-195
20	4	RO	OCH ₂ C ₆ H ₅	-#:	-CH ₃	153-155
	5	Ю	NHC6H5	-8	-CH ₃	193-194
	6	HO	O(CH ₂) ₂ Ph	-11	-CH ₃	140-145
	7	HO	cyclopentyl	-8	-CH ₃	164-166
	8	HO	1-pyrroly1	-H	-CH ₃	162-163
25	9	H ₂ N	cyclchexyl	-1 1	-CH ₃	
	10	Me ₂ NCO ₂	cyclohexyl	- #	-CH ₃	112-115
30	11	НО	CH ₂ -cyclo- hexyl	-11	-сн ₃	
	12	Ю	propargyl	-t i	-CH ₃ .	150-170 (amorphous)
35	13	но	allyl	-#	-CH ₃	141-143
	14	RO	-(CH ₂) ₄ -		-CH ₃	155-158
	15	t-BuCO ₂	cyclohexyl	·-8	-CH ₃	110-112
	16	c ₆ H ₅ ∞ ₂	cyclohexyl	-11	-CH ₃	>300 (HCl)
40	17	Etoco,	cyclchexyl	-11	-CH ₃	
	18	сн₃∞2	allyl	-8	-CH ₃	180-181 (HC1)
	19	CH ₂ CO ₂	cyclohexyl	-1 1	-CH ₃	
	20	n-PrCO ₂	allyl	-11	-CH ₃	
45	21	но	3,3-(Me)2- allyl	-13	∗CH ₃	142-144 (maleate)
	22	НО	allyl	-11	-CH ₃	183-185

TABLE 6 (cont'd)

Compound No.	<u>R</u> 5	<u>R</u> 1	R ²	<u>R³</u>	m.p. °C
23	i-PrCO ₂	allyl	-11	-сн ₃	232-234 (HC1)
24	Ю	2-Me allyl	-H	-CH ₃	174-175
25	MeOCH ₂ CO ₂	allyl	-8	-сн ₃	190-192 (HC1)
26	сн₃∞2	3,3-diMe-2- allyl	-#1	-CH ₃	180-183 (dec.) (HC1)
27	POM o	allyl	-B	-сн ₃	156-159 (HC1)
28	HO .	2-butenyl (cis+trans)	-11	-CH ₃	
29	но	cyclopropyl- methyl	-ti	-сн ₃	
30	PhCO2CH2O	allyl	-1 1	-CH ₃	
31	4-iPrPhNHCO2	allyl	-13	-CH ₃	
32	4-EtoPhNHCO2	allyl	-#1	-сн ₃	

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While the present invention has been described in conjunction with the specific embodiments set torth above, many alternatives, modifications and variations thereof will be apparent to those of ordinary skill in 45 the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

POM = t-BuccoccH2O

Claims

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Cleims for the following Contracting States: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. A compound having the structural formula I

and the pharmaceutically acceptable salts thereof, wherein:

represents -XR6, -CH₂R8, cycloalkyl having 3 to 8 carbon atoms, cycloalkenyl having 5 to 8 carbon atoms.

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- represents -H or R1 and R2 together represent alkanediyl being a divalent, straight or R2 branched hydrocarbon chain having 1 to 6 carbon atoms;
 - R3 represents H, or straight or branched alkyl having 1 to 6 carbon atoms;
- represents H, halo, straight or branched alkyl having 1 to 6 carbon atoms, haloalkyl being e straight or branched alkyl having 1 to 6 carbon atoms substituted with 1 to 5 halo groups, or alkoxy (wherein the alkyl portion is a straight or branched alkyl having 1 to 6 carbon atoms):
 - represents -OR10, -N(R9) or -O+C(R7) +OCOR13;
 - represents H, straight or branched alkyl having 1 to 6 carbon atoms, cycloalkyl having 3 to 8 carbon atoms, cycloalkenyl having 5 to 8 carbon atoms, aralkyl (wherein the eryl portion is a unsubstituted or substituted phenyl wherein substituted phenyl represents phenyl mono- or di-substituted by alkyl, hydroxy, alkyxy, alkylthio, halo, trifluoromethyl or combinations thereof and the alkyl portion is a straight or branched alkyl having 1 to 6 carbon atoms), heteroarylalkyl (wherein the heteroaryl portion is an aromatic heterocyclic group having at least one O, S and/or N atom and the alkyl portion is a straight or branched alkyl having 1 to 6 carbon atoms), haloalkyl being a straight or branched alkyl having 1 to 6 carbon atoms substituted with 1 to 5 halo groups, straight or branched alkenyl having 1 to 6 carbon atoms, alkynyl having 2 to 6 carbon atoms, cycloalkylalkyl (wherein the cycloalkyl portion is a cycloalkyl having 3 to 8 carbon atoms and the alkyl portion is a straight or branched alkyl having 1 to 6 carbon atoms), cycloalkenylalkyl (wherein the cycloalkenyl portion is a cycloalkenyl having 5 to 8 carbon atoms and the alkyl portion is a straight or branched alkyl having 1 to 6 carbon atoms), or alkoxyalkyl (wherein both alkyl portions are straight or branched alkyls having 1 to 6 carbon atoms):
 - represents H, or straight or branched alkyl having 1 to 6 carbon atoms;
 - represents cycloalkyl having 3 to 8 carbon atoms, cycloalkenyl having 5 to 8 carbon etoms, cycloalkylalkyl (wherein the cycloylkyl portion is a cycloalkyl having 3 to 8 carbon atoms end the alkyl portion is e straight or branched alkyl having 1 to 6 carbon atoms) or cycloalkenylalkyl (wherein the cycloalkenyl portion is a cycloalkenyl having 5 to 8 carbon atoms and the alkyl portion is a straight or branched alkyl having 1 to 6 carbon atoms):

independently represents H, straight or branched alkyl having 1 to 6 carbon atoms, each R⁹ alkoxy (wherein the alkyl portion is e straight or branched alkyl having 1 to 6 carbon atoms), alkoxyalkyl (wherein both alkyl portions are straight or branched elkyls heving 1

to 6 carbon atoms), arallyl (wherein the anyl portion is an unsubstituted or substituted phenryl wherein a budstituted phenryl represents phenryl mono- or dis-ubstituted by allyl, hydroxy, alkory, allytthio, halo, trifluoromethyl or combinations thereof and the allyl portion is e straight or branched allyl having 1 to 6 carbon atoms) or anyl being an unsubstituted or substituted phenryl group wherein substituted phenryl presents phenryl mono- or dis-ubstituted by alkyl, hydroxy, alkory, alkythio, halo, trifluoromethyl or combinations thereof:

- R¹⁰ represents H, -COR⁹ or CON(R⁹)₂;
- R¹³ represents straight or branched alkyl having 1 to 6 carbon atoms, asikyl (wherein the aryl portion is an unsubstituted or substituted phenyl wherein substituted phenyl represents phenyl monor or di-substituted by a hypidoxy, alkoyya, alkyliho, hako, triflucomethyl or combinations thereof and the alkyl portion is a straight or branched alkyl having 1 to 6 carbon atoms) or ary being an unsubstituted or substituted phenyl group wherein substituted phenyl represents phenyl mono- or di-substituted by alkyl, hydroxy, alkoyx, alkyliho, hako, this/uncomethyl or combinations thereof.
 - X represents -O- or -S-;
 - m represents 0 or 1;
 - Y represents N or CH:
 - Z represents CH₂ (if Y does not represent CH) or NR⁹; and
- p and q each independently represent integers of from 1 to 3 such that the sum of p plus q is from 1 to 5 and p and q do not both represent 1 when Y is N and Z is NR⁹.
- 2. A compound according to claim 1 wherein R1 represents XFF, CHRR, cycloality1 hering 3 to 8 carbon atoms or cycloalitynt having 5 to 8 carbon atoms, wherein X represents -0, or -5. FF represents straight or branched alky1 having 1 to 6 carbon atoms, cycloally1 having 3 to 8 carbon atoms, arally1 (wherein the sryl portion is a unsubstituted or substituted phenyl and the alkyl portion is estinght or branched alky1 hering 1 to 6 carbon atoms, absoluty being a tasking to branched alky1 having 1 to 6 carbon atoms and FF represents cycloality having 3 to 8 carbon atoms and FF represents cycloality having 3 to 8 carbon atoms and FF represents cycloality having 3 to 8 carbon atoms and FF represents cycloality having 3 to 8 carbon atoms and FF archarded alky1 portions are straight or tranched alky1 portion atoms.
 - 3. A compound according to claim 2, wherein R1 represents cyclohexyl or cyclohexenyl.
- as 4. A compound eccording to claim 1 wherein R1 represents



or pyrrolyl where m is 1 and R9 represents H, or straight or branched alkyl having 1 to 6 carbon atoms.

- 45 5. A compound according to any of the preceding claims, wherein R3 represents -CH3.
 - 6. A compound according to any of the preceding claims, wherein R* represents halo, preferably chloro, and R* represents -OH, -COO-Fe or -O-CIP\$ y-O-CORP\$ where R* represents straight or branched alityl having 1 to 6 carbon atoms, alloxy (wherein the altry) portion is a straight or branched alityls having 1 to 6 carbon atoms) or alloxyslally (wherein both ality) portions are straight or branched alityls having 1 to 6 carbon atoms). R* represents H and R* represents straight or branched alityl having 1 to 6 carbon atoms). R* represents H and R* represents straight or branched alityl having 1 to 6 carbon.
 - A compound according to claim 1, said compound being selected from:

 B-chioro-5-methoxy-3-methyl-2.3,4-5-testahydro-1H-3-benzazepine-7-ol,
 B-chioro-5-ethoxy-3-methyl-2.3,4-5-testahydro-1H-3-benzazepine-7-ol,
 B-chioro-5-ethylthio-3-methyl-2.3,4-5-testahydro-1H-3-benzazepine-7-ol,
 7-shioro-5-dimethyl-2.3,movl-1-ethoxy-methyl-2.3,5-testahydro-1H-3-benzazepine,

8-chloro-3-methyl-5-(1-piperidinyl)-2,3,4,5-tetrahydro-1H-3-benzazepine-7-ol, 8-chloro-5-cyclohexyl-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine-7-ol, 8-chloro-5-cyclohexyloxy-3-methyl-2,3.4,5-tetrahydro-1H-3-benzazepine-7-ol. 8-chloro-5-(2-cyclohexenyl)-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine-7-ol, 8-chloro-5-allyl-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine-7-ol, 8-chloro-5-(2,2,2-trifluoroethoxy)-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine-7-ol, 8-chloro-5-benzyloxy-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine-7-ol, 8-chloro-5-(phenethyloxy)-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine-7-ol, 8-chloro-5-(1-pyrrolyl)-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine-7-ol, 8-chloro-7-hydroxy-3-methyl-2,3,4,5-tetrahydrospiro [1H-3-benzazepine-5,5'-cyclopentane], 8-chloro-7-(ethoxy-formyloxy)-5-cyclohexyl-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine, 8-chloro-7-(isopropyl-formytoxy)-5-allyl-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine, 8-chloro-7-(methoxy-acetoxy)-5-allyl-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine, 8-chloro-7-acetoxy-5-(3-methyl-2-butenyl)-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine, 8-chloro-7-(t-butyroxy-methoxy)-5-allyl-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine, and the pharmaceutically acceptable salts of the foregoing.

 A process for the preparation of a compound of the formula I set forth in claim 1 which process comprises a process selected from the following processes A to E:

A: reduction of a carbonyl compound of the general formula:

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B: reduction of an ester of the general formula:

C: reduction at the double bond of a salt of the general formula:

D: intramplecular condensation of a compound of the general formula:

with elimination of HD and formation of the azepine ring, reduction at the olefinic double bond of a compound of the general formula:

s wherein in the foregoing formulae the dotted line in the azepine ring represents a faculative double bond, RI, RR, RR, RR and RI are as defined in claim 1, RR is RR or COORR, RR RR RR as defined in claim 1 or is alloxy (wherein the alkyl portion is a straight or branched alkyl having 1 to 6 carbon atoms), LP is an anion, preferably an anion derived from a halo acid or a suthoric acid, D is a reactive group capable of being eliminated as DH with formation of the azepine ring, and Z is RY or RR.

said process being followed as desired by one or more of the following faculative steps:

(i) removal of any protecting group present at the nitrogen atom,
 (ii) alkylation at the nitrogen atom wherein R₂ is hydrogen to introduce R² being alkyl,

(iii) etherification or thioetherification of \mathbf{R}^t wherein \mathbf{R}^t is -OH and \mathbf{R}^t is H to give a corresponding ether or thiol,

(iv) esterification of R5 wherein R5 is -OH, (v) halogenation of R4 where R4 is H,

 (vi) hydroxymethylation of R⁴ wherein R⁴ is H, followed by reduction of the so-introduced hydroxymethyl group to methyl,

and before or after said faculative step or steps, dealitylation of R⁶s where R⁵s is alkoxy, the so-obtained compound of the formula I being isolated in free form or in the form of a pharmaceutically ecceptable sait.

9. A compound of the formula II

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and the pharmaceutically acceptable salts thereof, wherein:

Q represents H, halo or -OSO₂R" wherein R" is CH₃, CF₃, phenyl or tolyl;

represents H, straight or branched alkyl having 1 to 6 carbon atoms, or COOR1* wherein R¹⁴ is straight or branched alkyl having 1 to 6 carbon atoms, anyl being an unsubstituted or substituted phenyl group wherein substituted phenyl represents plenyl mono- or dis-inbstituted by alkyl, hydroxy, alkoyr, alkylthio, halo, trifluoromethyl or

combinations thereof, arallyl (wherein the anyl portion is an unsubstituted or substituted phenyl wherein substituted phenyl represents phenyl mono- or disubstituted by sellyl, hydroxy, altoxy, altoxy, altoythin, halo, trifluoremethyl or combinations thereof and the allyl portion is a straight or branched skyl having 1 to 6 carbon atmos) or halashly being a straight or branched allyl having 1 to 6 carbon, atoms substituted with 1 to 5 halo groups.

- represents H, halo, straight or branched alkyl having 1 to 6 carbon atoms, haloalkyl being a straight or branched alkyl having 1 to 6 carbon atoms substituted with 1 to 5 halo groups, or alkoxy (wherein the alkyl portion is a straight or branched alkyl having 1 to 6 carbon atoms:
- R³⁴ represents -OR¹⁹, -N(R³)₂, -O-C(R²)₂-OCOR¹³ or alkoxy (wherein the alkyl portion is a straight or branched alkyl having 1 to 6 carbon atoms); where R² represents H, or straight or branched alkyl having 1 to 6 carbon atoms;
- each R² independently represents H, straight or branched alkyl having 1 to 6 carbon atoms, allowy (wherein the alkyl portions is a staight or branched alkyl having 1 to 8 carbon atoms); altoxyalkyl (wherein both alkyl portions are straight or branched alkyls having 1 to 8 carbon atoms, arably (wherein the arty portions is an unsubstituted or substituted phenyl represents phenyl mone or disubstituted by alkyl, hydroxy, alkoxy, alklythic, hab, titiscremetty or combinations thereof and the alkyl portion is a straight or branched alkyl having 1 to 6 carbon atoms) or any being an unsubstituted or substituted phenyl represents phenyl mone- or disubstituted by alkyl, hydroxy, alkoxy, alklythio, hab, titriturous therein substituted phenyl represents phenyl mone- or disubstituted by alkyl, hydroxy, alkoxyl, alkythio, hab, trifluoromethyl or combinations thereof.
- R° represents H. -COR® or -CON(R®);: and
 R³ represents straight or branched alleyl having 1 to 8 carbon atoms, aralkyl (wherein the
 anyl portion is an unsubstituted or substituted phenyl (wherein substituted phenyl
 represents phenyl mone- or dissubstituted by allyl, hydroxy, allxoy, allylylinio, halo,
 trifluorometryl or combinations hereoly and the alikyl potents is a straight or branched
 aliky having 1 to 8 carbon atoms) or anyl being an unsubstituted or substituted or phenyl
 group (wherein substituted phenyl represents phenyl mone- or dissubstituted by allyl).
 - hydroxy, alkoxy, alkythio, halo, trifluoromethyl or combinations thereof);

 10. A pharmaceutical composition comprising as active ingredient a compound as claimed in any one of claims 1 to 7 together with a pharmaceutically acceptable carrier.
 - 11. The use of a compound as claimed in any one of claims 1 to 7 for the preparation of a pharmaceutical composition for use in treatment of psychoses or depression, or for effecting analgosis, in particular for use as a natiosychotic.
- 40 Claims for the following Contracting State : ES

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1. A process for-the preparation of a compound of the formula I

and the pharmaceutically acceptable salts thereof, wherein:

R¹ represents -XR⁶, -CH₂R⁶, cycloalkyl having 3 to 8 carbon atoms, cycloalkenyl having 5 to 8 carbon atoms.

or pyrrolyl;

12 represents -H or R¹ and R² together represent alkanediyl being a divalent, straight or branched hydrocarbon chain having 1 to 6 carbon atoms;

R3 represents H, or straight or branched alkyl having 1 to 6 carbon atoms;
R4 represents H, halo, straight or branched alkyl having 1 to 6 carbon

represents H, halo, straight or branched alkyl having 1 to 6 carbon atoms, haloalkyl being a straight or branched alkyl having 1 to 6 carbon atoms substituted with 1 to 5 halo groups, or alkoxy (wherein the alkyl portion is a straight or branched alkyl having 1 to 6 carbon atoms):

R⁵ represents -OR¹⁰, -N(R³)₂ or -O·C(R⁷)₂ •OCOR¹³;
R⁶ represents H. straight or branched alkyl having 1.1

represents H, straight or branched alkyl having 1 to 6 carbon atoms, cycloalkyl having 3 to 8 carbon atoms, cycloalkenyl having 5 to 8 carbon atoms, aralkyl (wherein the sryl portion is a unsubstituted or substituted phenyl wherein substituted phenyl represents phenyl mono- or di -substituted by alkyl, hydroxy, alkoxy, alkylthio, halo, trifluoromethyl or combinations thereof and the alkyl portion is e straight or branched alkyl having 1 to 6 carbon atoms), heteroarylalkyl (wherein the heteroaryl portion is an aromatic heterocyclic group having at least one O, S and/or N atom and the alkyl portion is a straight or branched alkyl having 1 to 6 carbon atoms), haloalkyl being a straight or branched alkyl having 1 to 6 carbon atoms substituted with 1 to 5 halo groups, straight or branched alkenyl having 1 to 6 carbon atoms, alkynyl having 2 to 6 carbon atoms. cycloalkylalkyl (wherein the cycloalkyl portion is a cycloalkyl having 3 to 8 carbon atoms and the alkyl portion is a straight or branched alkyl having 1 to 6 carbon atoms), cycloalkenylalkyl (wherein the cycloalkenyl portion is a cycloelkenyl having 5 to 8 carbon etoms and the elkyl portion is e straight or branched alkyl heving 1 to 6 carbon atoms), or elkoxyelkyl (wherein both alkyl portions are straight or branched alkyls having 1 to 6 carbon atoms):

represents H. or straight or branched alkyl having 1 to 6 carbon etoms:

represents cyclosially having 3 to 8 carbon stoms, cyclosially having 5 to 8 carbon atoms, cyclosially fiverier the cycloylity prior in is a cyclosity having 3 to 8 carbon atoms and the alkyl portion is a straight or branched slay! having 1 to 8 carbon atoms and the alkyl portion is a straight or branched slay! having 1 to 6 carbon atoms or cyclosialenylately (wherein the cyclosialeny) portion is e cyclosialenyl having 5 to 8 carbon atoms and the alkyl portion is a straight or branched alkyl having 1 to 6

caron atoms; independently represents H, straight or branched alkyl having 1 to 6 carbon stoms, alkoxy (wherein the alkyl portion is a straight or branched alkyl having 1 to 6 carbon stoms), alkoxyliky (wherein both alkyl portions are straight to rbranched alkyls having 1 to 6 carbon atoms), alkoxyliky (wherein both alkyl portion is an unsubstituted alkyls having 1 to 6 carbon atoms), arallyl (wherein the anyl portion is an unsubstituted or substituted phenyl wherein substituted phenyl represents phenyl mono- or dis-ubstituted by alkyl, hydroxy, alkythio, halo, tilluoromethyl or combinations thereof and the alkyl portion is e straight or branched alkyl having 1 to 6 cerbon atoms) or anyl being an unsubstituted or substituted phenyl represents phenyl mono- or dis-ubstituted by eltyl, hydroxy, alkyylikio, halo, trilluoromethyl or combinations thereos

R10 represents H. -COR9 or -CON(R9 b:

represents Price of the Control of t

represents -O- or -S-; represents 0 or 1;

R8

each R⁹

R13

X m

represents N or CH;

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Z represents CH₂ (if Y does not represent CH) or NR⁹; and

p and q each independently represent integers of from 1 to 3 such that the sum of p plus q is from 1 to 5 and p and q do not both represent 1 when Y is N and Z is NR3,

which process comprises a process selected from the following processes A to E:

A: reduction of a carbonyl compound of the general formula:

$$R^{5\alpha}$$

$$R^{5\alpha}$$

$$R^{1}$$

$$R^{2}$$

$$R^{2}$$

B: reduction of an ester of the general formula:

C: reduction at the double bond of a salt of the general formula:

D: intramolecular condensation of a compound of the general formula:

with elimination of HD and formation of the azepine ring,

E: reduction at the olefinic double bond of a compound of the general formula:

wherein in the toragoing formulae the dotted line in the azepine ring represents a faculative double bond, R¹, R², R³, R³, A³ and R¹³ are as defined above, R¹⁵ is R³ or COOR¹³, R⁵ is R³ as defined above or is allowy (wherein the alkyl portion is a straight or branched alkyl hawing 1 to 6 carbon atoms), L³ is an anion, preferably an anion derived from a halo acid or a sulfinic acid, D is a ready group capable of being eliminated as DH with formation of the azepine ring, and Z is R³ to R³.

said process being followed as desired by one or more of the following faculative steps:

(i) removal of any protecting group present at the nitrogen atom,

(ii) alkylation at the nitrogen atom wherein R₃ Is hydrogen to introduce R³ being alkyl,

(iii) etherification or thioetherification of R1 wherein R1 is -OH and R2 is H to give a corresponding ether or thiol.

(iv) esterification of R5 wherein R5 is -OH,

(v) halogenation of Rt where Rt is H,

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(vi) hydroxymethylation of R⁴ wherein R⁴ Is H, followed by reduction of the so-introduced hydroxymethyl group to methyl,

and before or after said faculative step or steps, dealkylation of R5a where R5a is alkoxy,

the so-obtained compound of the formula I being Isolated in free form or in the form of a pharmaceutically acceptable salt.

- 2. A process according to claim 1 wherein R1 represents XMF, CHyR1, cycloally/ having 3 to 8 carbon atoms or cycloallevyl having 5 to 8 carbon atoms, wherein X represents Co. 76. PF represents straight or branched alkyl having 1 to 6 carbon atoms, cycloalkyl having 3 to 8 carbon atoms, aralkyl (wherein the ary) portion is an unsatituded or substituted phenyl and the alkyl portion is at straight or branched alkyl having 1 to 6 carbon atoms, alkalyl being a traight or branched alkyl having 1 to 8 carbon atoms and Prepresents cycloalkyl having 5 to 8 carbon atoms and Prepresents cycloalky having 5 to 8 carbon atoms and Prepresents cycloalky having 5 to 8 carbon atoms and Prepresents cycloalky having 5 to 8 carbon atoms and Prepresents cycloalky having 5 to 8 carbon atoms and Prepresents cycloalky having 5 to 8 carbon atoms and Prepresents cycloalky having 5 to 8 carbon atoms or alkoxyalkyl (wherein both akyl portions are straight or branched alkyls having 5 to 8 carbon atoms or alkoxyalkyl (wherein both akyl portions are straight or branched alkyls having 1 to 6 carbon atoms.
- 3. A process according to claim 2, wherein R¹ represents cyclohexyl or cyclohexenyl.
- 4. A process according to claim 1 wherein R1 represents

or pyrrolyl where m is 1 and R⁹ represents H, or straight or branched alkyl having 1 to 6 carbon atoms.

- 5. A process according to any of the preceding claims, wherein R3 represents -CH3.
- A process according to any of the preceding claims, wherein R* expresents halo, preferably chloro, and R* represents 5-UH, COCP R* or -0-CR*Ps, 2-OCR*D* where R* represents straight or branched alilyl having 1 to 8 carbon atoms, alknow (wherein the alicyl portion is a straight or branched alilyl having 1 to 8 carbon atoms) or alknowsyld (wherein both slight portions are straight or branched alilyl having 1 to 6 carbon atoms), R* represents H and R*D* represents straight or branched alilyl having 1 to 8 carbon atoms.

A process according to claim 1, wherein the produced compound is salected from:
 B-chicro-S-methays-3-methyle 23,4,5-fetrahydro-114-3-benzzaepine-7-ol,
 B-chicro-S-ethony-3-methyle 23,4,5-fetrahydro-114-3-benzzaepine-7-ol,
 B-chicro-S-ethyllrio-3-methyle 23,4,5-fetrahydro-114-3-benzzaepine-7-ol,
 7-chicro-S-dimethylca-thon-1-t-ethoxy-methyl-23,4,5-fetrahydro-114-3-benzzaepine-7-ol,
 B-chicro-3-methyl-5-f1-piperidimylp/23,4,5-fetrahydro-114-3-benzzaepine-7-ol,
 B-chicro-S-cycloheny-3-methyl-23,4,5-fetrahydro-114-3-benzzaepine-7-ol,
 B-chicro-3-methyl-5-cycloheny-3-methyl-23,4,5-fetrahydro-114-3-benzzaepine-7-ol,
 B-chicro-3-cycloheny-3-methyl-23,4,5-fetrahydro-114-3-benzzaepine-7-ol,
 B-chicro-3-cycloheny-3-methyl-23,4,5-fetrahydro-114-3-benzzaepine-7-ol,

8-chloro-5-cyclohexyl-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine-7-ol, 8-chloro-5-cyclohexyloxy-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine-7-ol, 8-chloro-5-(2-cyclohexenyl)-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine-7-ol, 8-chloro-5-allyl-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine-7-ol,

8-chloro-5-(2,2,2-trifluoroethoxy)-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine-7-ol, 8-chloro-5-benzyloxy-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine-7-ol, 8-chloro-5-(obensthoxy)-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine-7-ol,

8-chloro-5-(1-pyrrolyl)-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine-7-ol, 8-chloro-7-hydroxy-3-methyl-2,3,4,5-tetrahydrospiro[1H-3-benzazepine-5,5'-cyclopentane],

8-chloro-7-hydroxy-3-methyl-2,3.4,5-tetrahydrospirof.1H-3-benzazepine-5,5"-cyclopentane], 8-chloro-7-(ethoxy-tormyloxy)-5-cyclobay-1-amethyl-2,3.4,5-tetrahydro-1H-3-benzazepine, 8-chloro-7-(isopropyl-formyloxy)-5-allyl-3-methyl-2,3.4,5-tetrahydro-1H-3-benzazepine, 8-chloro-7-fraethoxy-acetoxyl-5-allyl-3-methyl-2,3.4,5-tetrahydro-1H-3-benzazepine, 9-chloro-7-fraethoxy-acetoxyl-5-allyl-3-methyl-2,3.4,5-tetrahydro-1H-3-benzazepine, 9-chloro-7-fraethoxy-acetoxyl-5-allyl-3-methyl-2,3.4,5-tetrahydro-1H-3-benzazepine, 9-chloro-7-fraethoxy-acetoxyl-5-allyl-3-methyl-2,3.4,5-tetrahydro-1H-3-benzazepine, 9-chloro-7-fraethoxyl-6-dishyl-3-methyl-2,3.4,5-tetrahydro-1H-3-benzazepine, 9-chloro-7-fraethoxyl-6-dishyl-

8-chioro-7-acotoxy-5-(3-methyl-2-butenyl)-3-methyl-2.3,4.5-tetrahydro-1H-3-benzazepine, 8-chioro-7-(1-butyroxy-methoxy)-5-allyl-3-methyl-2.3,4.5-tetrahydro-1H-3-benzazepine, and the pharmacoutically acceptable salts of the foregoing.

8. A process for the preparation of a compound of the formula II

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and the pharmaceutically acceptable salts thereof, wherein:

F3a

each R³

Q represents H, halo or -OSO₂R" wherein R" is CH₂, CF₃, phenyl or tolyl;

represents H, hallo or -US-SH* wineren H is UHB, UMB, progress H, hallo or -US-SH* wineren H is UHB, UMB, progress H, hallo or -US-SH* wherein R* is straight or branched alkyl having 1 to 8 carbon atoms, and being an unsubstituted or substituted phenyl group wherein substituted phenyl represents phenyl mone- or dis-ubstituted by alkyl, hydroxa, alkoxy, although alkyl in the progress H is the progress H is

groups:
represents H, halo, straight or branched allof having 1 to 6 carbon atoms, haloallof being a straight or branched allof having 1 to 6 carbon atoms substituted with 1 to 5 halo groups, or allowy (wherein the allof portion is a straight or branched allof having 1 to 6 carbon atoms.

R5* represents -OR*0, -N(R*)_k, -O-C(R*)_k-OCOR*0 or allowy (wherein the alkyl portion is a straight or branched alkyl having 1 to 6 carbon atoms); where R* represents H, or straight or branched alkyl having 1 to 6 carbon atoms;

Independently represents H. straight or branched allynched livynched livynched livynched allynched allynch

mono- or di-substituted by alkyl, hydroxa, alkoxy, alkylthio, halo, trifluoromethyl or combinations thereof;

R10 represents H, -COR9 or -CON(R9)2; and

R¹³ represents straight or branched alley! having 1 to 6 carbon atoms, analley! (wherein he any! portion is an unsubstituted or substituted pheny! (wherein substituted pheny! represents pheny! mone or 6-substituted by alley!, hydroxy, alloxy, alleythio, halo, trifluocomethy! or combinations thereof) and the alley! portion is a straight or branched alky! having 1 to 6 carbon atoms) or any being an unsubstituted or substituted pheny! group (wherein substituted pheny! represents pheny! mone- or dissubstituted by alky!, hydroxy, alkoxy, alkityhi, halo, infuturomethy or combinations thereof):

which process comprises halogenating the compound of formula VIII

to produce a compound of formula II wherein Q represents halo; and subsequent hydrolyzation to a OH group and reaction with an sulfonyl halide or anhydride to produce a compound of the formula II wherein Q is -OSO, FF.

25 9. A process for preparing a pharmaceutical composition, which comprises admixing as active ingredient a compound prepared in accordance with any one of claims 1 to 7 with a pharmaceutically acceptable carrier.

Claims for the following Contracting State : GR

1. A compound having the structural formula I

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and the pharmaceutically acceptable salts thereof, wherein:

represents -XR⁶, -CH₂R⁸, cycloalkyl having 3 to 8 carbon atoms, cycloalkenyl having 5 to 8 carbon atoms.

or pyrrolyl;

R² represents -H or R¹ and R² together represent alkanediyl being a divalent, straight or branched hydrocarbon chain having 1 to 6 carbon atoms;

R3 represents H, or straight or branched alkyl having 1 to 6 carbon atoms;

R⁴ represents H, halo, straight or branched alkyl having 1 to 6 carbon atoms, haloalkyl being a straight or branched skyl having 1 to 6 carbon atoms substituted with 1 to 5 halo groups, or alkoxy (wherein the alkyl portion is a straight or branched alkyl having 1 to 6 carbon atoms);

R⁵ represents -OR¹⁰, -N(R⁹), or -O-C(R⁷), -OCOR¹³;

represents H, straight or branched alkyl having 1 to 6 carbon atoms, cycloalkyl having 3 to 8 carbon atoms, cycloalkenyl having 5 to 8 carbon atoms, aralkyl (wherein the aryl portion is a unsubstituted or substituted phenyl wherein substituted phenyl represents phenyl mono- or di-substituted by alkyl, hydroxy, alkoxy, alkylthio, halo, trifluoromethyl or combinations thereof and the alkyl portion is a straight or branched alkyl having 1 to 6 carbon atoms), heteroarylalkyl (wherein the heteroaryl portion is an aromatic heterocyclic group having at least one O, S and/or N atom and the alkyl portion is a straight or branched alkyl having 1 to 6 carbon atoms), haloalkyl being a straight or branched alkyl having 1 to 6 carbon atoms substituted with 1 to 5 halo groups, straight or branched alkenyl having 1 to 6 carbon atoms, alkynyl having 2 to 6 carbon atoms, cycloalkylalkyl (wherein the cycloalkyl portion is a cycloalkyl having 3 to 6 carbon atoms and the alkyl portion is a straight or branched alkyl having 1 to 6 carbon atoms). cycloalkenylalkyl (wherein the cycloalkenyl portion is a cycloalkenyl having 5 to 8 carbon atoms and the alkyl portion is a straight or branched alkyl having 1 to 6 carbon atoms), or alkoxyalkyl (wherein both alkyl portions are straight or branched alkyls having 1 to 6 carbon atoms):

represents H. or straight or branched alkyl having 1 to 6 carbon atoms: P8

represents cycloalkyl having 3 to 8 carbon atoms, cycloalkenyl having 5 to 8 carbon atoms, cycloalkylalkyl (wherein the cycloylkyl portion is a cycloalkyl having 3 to 8 carbon atoms and the alkyl portion is a straight or branched alkyl having 1 to 6 carbon atoms) or cycloalkenylalkyl (wherein the cycloalkenyl portion is a cycloalkenyl having 5 to 8 carbon atoms and the alkyl portion is a straight or branched alkyl having 1 to 6 carbon atoms):

each R⁹ independently represents H. straight or branched alkyl having t to 6 carbon atoms. alkoxy (wherein the alkyl portion is a straight or branched alkyl having t to 6 carbon atoms), alkoxyalkyl (wherein both alkyl portions are straight or branched elkyls having 1 to 6 carbon atoms), aralkyl (wherein the aryl portion is an unsubstituted or substituted phenyl wherein substituted phenyl represents phenyl mono- or di-substituted by alkyl, hydroxy, alkoxy, alkylthio, halo, trifluoromethyl or combinations thereof and the alkyl portion is a straight or branched alkyl having 1 to 6 carbon atoms) or aryl being an unsubstituted or substituted phenyl group wherein substituted phenyl represents phenyl mono- or di-substitinted by alkyl, hydroxy, alkoxy, alkylthio, halo, trifluoromethyl or combinations thereof:

represents H. -COR3 or -CON(R3):

R13 represents straight or branched alkyl having 1 to 6 carbon atoms, aralkyl (wherein the aryl portion is an unsubstituted or substituted phenyl wherein substituted phenyl represents phenyl mono- or di-substituted by alkyl, hydroxy, alkoxy, alkylthio, halo, trifluoromethyl or combinations thereof and the alkyl portion is a straight or branched alkyl having 1 to 6 carbon atoms) or anyl being an unsubstituted or substituted phenyl group wherein substituted phenyl represents phenyl mono- or di-substituted by alkyl, hydroxy, alkoxy, alkylthio, halo, trifluoromethyl or combinations thereof.

х represents -O- or -S-:

m represents 0 or 1;

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represents N or CH;

represents CH2 (if Y does not represent CH) or NR9; and

z each independently represent integers of from 1 to 3 such that the sum of p plus q is from 1 to 5 and p and q do not both represent 1 when Y is N and Z is NR9.

2. A compound according to clarn 1 wherein R1 represents -XR6, - CH2R8, cycloalkyl having 3 to 8 carbon atoms or cycloalkenyl having 5 to 8 carbon atoms, wherein X represents -O-, or -S-, R5 represents straight or branched alkyl having 1 to 8 carbon atoms, cycloalkyl having 3 to 8 carbon atoms, aralkyl (wherein the aryl portion is an unsubstituted or substituted phenyl and the alkyl portion is a straight or branched alkyl having 1 to 6 carbon atoms), haloalkyl being a straight or branched alkyl having 1 to 6 carbon atoms substituted with 1 to 5 halo groups, or alkoxyalkyl (wherein both alkyl portions are straight or branched alkyls having 1 to 6 carbon atoms and R® represents cycloalkyl having 3 to 8 carbon atoms, cycloalkenyl having 5 to 8 carbon atoms or alkoxyalkyl (wherein both alkyl portions are straight or branched alkyls having 1 to 6 carbon atoms.

- 3. A compound according to claim 2, wherein R1 represents cyclohexyl or cyclohexenyl.
- 4. A compound according to claim 1 wherein R1 represents

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or pyrrolyl where m is 1 and R9 represents H, or straight or branched alkyl having 1 to 6 carbon atoms.

- 5. A compound according to any of the preceding claims, wherein R3 represents -CH3.
- 15. 6. A compound according to any of the preceding claims, wherein R* operatins halo, preferably chloro, and R* inspensents. OH. OCO.R* or O-O.CR* in O-O.CR* of Preparents statistic transmission also having 1 to 6 carbon atoms, allowy (wherein the alty) portion is a straight or branched allry having 1 to 6 carbon atoms, allowy (wherein the alty) portion is a straight or branched allry having 1 to 6 carbon atoms). R* represents H and R*P represents straight for branched allrys having 1 to 6 carbon atoms.
 - 7. A compound according to claim 1, said compound being selected from: B-chloro-5-methoxy-3-methyl-2.3.4.5-tetrahydro-1H-3-benzazepine-7-ol, B-chloro-5-ethoxy-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine-7-ol, 8-chloro-5-ethylthio-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine-7-ol, 7-chloro-8-dimethylcarbamoyl-1-ethoxy-methyl-2,3.4,5-tetrahydro-1H-3-benzazepine, 8-chloro-3-methyl-5-(1-piperidinyl)-2,3,4,5-tetrahydro-1H-3-benzazepine-7-ol, 8-chloro-5-cyclohexyl-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazeplne-7-ol, B-chloro-5-cyclohexyloxy-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine-7-ol, B-chloro-5-(2-cyclohexenyl)-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine-7-ol, 8-chloro-5-allyl-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine-7-ol, 8-chloro-5-(2,2,2-trifluoroethoxy)-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine-7-ol, 8-chloro-5-benzyloxy-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine-7-ol, 8-chloro-5-(phenethyloxy)-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine-7-ol, 8-chloro-5-(1-pyrrolyl)-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine-7-ol, B-chloro-7-hydroxy-3-methyl-2,3,4,5-tetrahydro-spiro [1H-3-benzazepine-5,5'-cyclopentane], 8-chloro-7-(ethoxy-formyloxy)-5-cyclohexyl-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine, 8-chloro-7-(isopropyl-formyloxy)-5-allyl-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine, 8-chloro-7-(methoxy-acetoxy)-5-allyl-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine, 8-chloro-7-acetoxy-5-(3-methyl-2-butenyl)-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine, 8-chloro-7-(t-butyroxy-methoxy)-5-allyl-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine,
 - 8. A process for the preparation of a compound of the formula I set forth in claim 1 which process comprises a process selected from the following processes A to E:
 - A: reduction of a carbonyl compound of the general formula:

and the pharmaceutically acceptable salts of the foregoing.

B: reduction of an ester of the general formula

10 C: reduction at the double bond of a salt of the general formula:

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D: intramolecular condensation of a compound of the general formula:

with elimination of HD and formation of the azepine ring, E: reduction at the olefinic double bond of a compound of the general formula:

wherein in the foregoing formulae the dotted line in the azeptine ring represents a faculative double bond, RI, RR, RP, RP and RP are as defined in claim 1, RP is RP or COORP3, RP is RP as defined in claim 1 or is allowy (wherein the ally) potton is a straight for transchad alily) having 1 to 6 carbon atoms), LP is an anion, preferably an anion derived from a halo acid or a sulforic acid, D is a reactive group capable of being eliminated as DH with formation of the aceptine ring, and 2 is RP or RP, said process being followed as desired by one or more of the following faculative steps:

- (i) removal of any protecting group present at the nitrogen atom,
 - (ii) alkylation at the nitrogen atom wherein R₂ is hydrogen to introduce R³ being alkyl,
 - (iii) etherification or thioetherification of RI wherein RI is -OH and RI is H to give a corresponding other or thiol.
 - (iv) esterification of R5 wherein R5 is -OH.

- (v) halogenation of R4 where R4 is H,
- (vi) hydroxymethylation of R⁴ wherein R⁴ is H, followed by reduction of the so-introduced hydroxymethyl group to methyl.
- and before or after said faculative step or steps, dealty/lation of R^{5e} where R^{5e} is alkoxy, the so-obtained compound of the formula I being isolated in free form or in the form of a pharmaceutically acceptable sait.
- 9. A compound of the formula II

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and the pharmaceutically acceptable salts thereof, wherein:

- Q represents H, halo or -OSO₂R" wherein R" is CH₃, CF₃, phenyl or tolyl;

 R^{3a} represents H, straight or branched alloy baying 1 to 6 carbon ator
 - Terpresents II, straight or branched alityl having 1 to 6 carbon atoms, or COORI⁴¹ whenin RI⁴¹ is straight or branched alityl having 1 to 6 carbon atoms, any bleng an unsubstituted or substituted phenyl group wherein substituted phenyl represents plenyl mone- or discussituted phenyl splenyl represents plenyl combinations thereot, arelityl (wherein the anyl portion is an unsubstituted or substituted phenyl wherein substituted phenyl represents phenyl mone- or discussituted by alityl, hydroxy, altxoxy, allythio, halo, tiflucorometry or combinations thereof and the alityl portion is a stealpit or branched alityl having t to 6 carbon atoms) or haloality being a straight or branched alityl having 1 to 6 carbon atoms substituted with 1 to 5 halo groups;
- R⁴ represents H, halo, straight or branched alkyl having 1 to 6 carbon etoms, haloalkyl being a straight or branched alkyl having 1 to 6 carbon atoms substituted with 1 to 5 halo groups, or alkoxy (wherein the alkyl portion is a straight or branched alkyl having 1 to 6 carbon atoms.)
 - R^{5a} represents -OR¹⁰, -N(R²)₂, -O-C(R²)₂-OCOR¹³ or alkoxy (wherein the alkyl portion is a straight or branched alkyl having 1 to 6 carbon atoms); where R² represents H, or straight or branched alkyl having 1 to 6 carbon atoms;
 - each R² independently represents H, stealpht or branched alkyl having 1 to 6 carbon atoms, alloy (wherein the alkyl portion is a straight to transhood alkyl having 1 to 6 carbon atoms), alkoyalkyl (wherein hoth alkyl portions are straight or branched alkyls having 1 to 6 carbon atoms), arallyl (wherein the any portion is an unsubstituted or substituted phenyl represents phenyl mone- or dis-substituted by alkyl, hydroxy, alkoxy, altylifich, halo, intiunomethyl or combinations thereof and the alkyl portion is a straight or branched alkyl having 1 to 6 carbon atoms) or anyl being an unsubstituted or substituted phenyl represents phenyl mone- or disubstituted party (presents phenyl mone- or disubstituted by alkyl, hydroxy, alkoxy, alkythio, halo, triturormethyl or combinations thereof
 - R¹⁰ represents H. -COR⁵ or -CON(R⁵); and
 - represents straight or branched altyl having 1-6 carbon atoms, arailyl (wherein the aryl portion is an unsubstituted or substituted phenyl (wherein substituted phenyl represents phenyl mono: or disabstituded by altyl, lydroxy, alloxy, altylifth, alto, Intilucromethyl or combinations thereoi) and the altyl portion is a straight or branched altyl having 1 to 6 carbon atoms) or anyl being an unsubstituted or substituted phenyl group (wherein substituted phenyl group (wherein substituted phenyl represents phenyl mono: or disabstituted by altyl, hydroxy, altoxy, altvitly, lab. (filtipomethri or combinations thereoil):
- A process for preparing a pharmaceutical composition which comprises admixing as active ingredient a compound as claimed in any one of claims 1 to 7 with a pharmaceutically acceptable carrier.

11. The use of a compound as claimed in any one of claims 1 to 7 for the preparation of e pharmaceutical composition for use in treatment of psychoses or depression, or for effecting analgesia, in particular for use as an antipsychotic.

5 Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Verbindung mit der Strukturformel I

und die pharmazeutisch annehmbaren Salze derselben, worin:

R¹ -XR⁶, -CH₂R⁸, Cycloalkyl mit 3 bis 8 Kohlenstoffatomen, Cycloalkenyl mit 5 bis 8 Kohlenstoffatomen.

oder Pyrrolyl bedeutet,

-H bedeutet oder R¹ und R² zusammen Alkandiyl bedeuten und eine zweiwertige, gerade oder verzweigte Kohlenwasserstoffkette mit 1 bis 6 Kohlenstoffatomen sind, H oder grades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstoffatomen bedeutet,

H, Halogen, gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstoffatomen, Halogenalkyl, das gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstoffatomen ist, welches mit 1 bis 5 Halogengruppen substituiert ist, oder Alkoxy bedeutet (worin der Alkylteil gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstoffatomen ist),

-OR10. -N(R9) oder -O • C(R7) > • OCOR19 bedeutet.

H, gerades oder verzweigtes Alkyl mit 1 bls 6 Kohlenstoffatomen, Cycloalkyl mit 3 bis 8 Kohlenstoffatomen, Cycloalkenyl mit 5 bis 6 Kohlenstoffatomen, Aralkyl (worin der Arytteil unsubstituiertes oder substituiertes Phenyl Ist, worin substituiertes Phenyl durch Alkyl, Hydroxy, Alkoxy, Alkylthio, Halogen, Trifluormethyl oder deren Kombinationen mono- oder disubstituiertes Phenyl bedeutet, und der Alkylteil gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstoffatomen ist), Heteroarylalkyl (worin der Heteroarylteil eine aromatische heterocyclische Gruppe mit wenigstens einem O-, S- und/oder N-Atom ist und der Alkylteil gerades oder verzweigtes Alkyl mit 1 bis B Kohlenstoffatomen ist), Halogenalkyl, das gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstoffen ist, das mit 1 bis 5 Halogengruppen substituiert ist, gerades oder verzweigtes Alkenyl mit 1 bis 6 Kohlenstoffatomen, Alkinyl mit 2 bis 6 Kohlenstoffatomen, Cycloalkylalkyl (worin der Cycloalkylteil Cycloalkyl mit 3 bis 6 Kohlenstoffatomen ist und der Alkylteil gerades oder verzweigtes Alkyt mit 1 bis 6 Kohlenstoffatomen ist), Cycloalkenylalkyl (worin der Cycloalkenylteil Cycloalkenyl mit 5 bis 8 Kohlenstoffatomen ist und der Alkylteil gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstoffatomen ist) oder Alkoxyalkyl (worin beide Alkylteile gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstoffatomen sind) bedeutet,

 bedeutet,

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R13

jeweils H, gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstoffatomen, Alkoxy (worin der Alkytteil gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstoffatomen ist), Alkoxyalkyl (worin beide Alkylteile gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstoffatomen sind), Aralkyl (wonn der Arytteil unsubstituiertes oder substituiertes Phenyl ist, wonn substituiertes Phenyl durch Alkyl, Hydroxy, Alkoxy, Alkylthlo, Halogen, Trifluormethyl oder deren Kombinationen mono- oder disubstituiertes Phenyl bedeutet, und der Alkylteil gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstoffatomen ist) oder Aryl bedeuten, das eine unsubstitulerte oder substituierte Phenylgruppe ist, wobei substituiertes Phenyl durch Alkyl, Hydroxy, Alkoxy, Alkylthio, Halogen, Trifluormethyl oder deren Kombinationen mono- oder disubstituiertes Phenyl bedeutet,

P10 H. -COR⁹ oder -CON(R⁹)₂ bedeutet.

gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstoffatomen, Aralkyl (worin der Arylteil innsubstituiertes oder substituiertes Phenyl ist, wobei substituiertes Phenyl durch Alkyl, Hydroxy, Alkoxy, Alkylthio, Halogen, Trifluormethyl oder deren Kombinationen monooder disubstituiertes Phenyl bedeutet, und der Alkylteil gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstoffatomen ist) oder Aryl bedeutet, das eine unsubstituierte oder substituierte Phenylgruppe ist, wobei substituiertes Phenyl durch Alkyl, Hydroxy, Alkoxy, Alkylthio, Halogen, Trifluormethyl oder deren Kombinationen mono- oder disubstituiertes Phenyl bedeutet.

X -O- oder -S- bedeutet,

0 oder 1 bedeutet, m

N oder CH bedeutet. 7

CH2 (falls Y nicht CH bedeutet) oder NR3 bedeutet und

leweils unabhängig ganze Zahlen von 1 bis 3 bedeuten, sodaß die Summe von p plus g p und a 1 bis 5 ist und p und g nicht beide 1 bedeuten, wenn Y N ist und Z NR⁹ ist.

- Verbindung gemäß Anspruch 1, wobei R¹ -XR², -CH-R², Cycloalkyl mit 3 bis 6 Kohlenstoffatomen oder Cycloalkenyl mit 5 bis 8 Kohlenstoffatomen bedeutet, worin X -O- oder -S- bedeutet, R⁶ gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstoffatomen, Cycloalkyl mit 3 bis 8 Kohlenstoffatomen, Aralkyl (worin der Arviteil unsubstituiertes oder substituiertes Phenyl ist und der Alkviteil gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstoffatomen ist), Halogenalkyl, das gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstoff ist, das mit 1 bis 5 Halogengruppen substituiert ist, oder Alkoxyalkyl bedeutet (wonn beide Alkylteile gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstoffatomen sind) und R⁸ Cycloalkyl mit 3 bis 8 Kohlenstoffatomen, Cycloalkenyl mit 5 bis 8 Kohlenstoffatomen oder Alkoxyalkyl (wonn beide Alkylteile gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstoffatomen sind) bedeuten.
- 3. Verbindung gemäß Anspruch 2, worin R1 Cyclohexyl oder Cyclohexenyl bedeutet.
- 4. Verbindung gemäß Anspruch 1, worin R1



oder Pyrrolyl bedeutet, wo m 1 ist, und R9 H oder gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstoffatomen bedeutet.

- Verbindung gemäß einem der vorangehenden Ansprüche, worin R3 -CH₃ bedeutet.
- 6. Verbindung gemäß einem der vorangehenden Ansprüche, worin R* Halogen, vorzugsweise Chlor, bedeutet und R5 -OH, -OCO-R9 oder -O-C(R7)2 -OCOR13 bedeutet, worin R9 gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstoffatomen, Alkoxy (worin der Alkylteil gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstoffatomen ist) oder Alkoxyalkyl (worin beide Alkylteile gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstoffatomen sind) bedeutet, R7 H bedeutet und R13 gerades oder verzweigtes Alkyl

mit 1 bis 6 Kohlenstoffatomen bedeutet.

- Verbindung gemäß Anspruch 1, wobei die Verbindung aus B-Chlor-S-methoxy-A-methyl-2,3,4,5-letahydro-IH-3-benzazepin-7-ol, B-Chlor-S-dihydrio-3-methyl-2,3,4,5-letahydro-IH-3-benzazepin-7-ol, B-Chlor-S-ethythio-3-methyl-2,3,4,5-letahydro-IH-3-benzazepin-7-ol, J-Chlor-S-ethydrio-3-methyl-2,3,4,5-letahydro-IH-3-benzazepin-7-ol, J-Chlor-S-ethydrio-3-methyl-2,3,4,5-letahydro-IH-3-benzazepin-7-ol,
 - 7-Chlor-8-dimethylcarbamoyl-1-ethoxy-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin, 8-Chlor-3-methyl-5-(1-pipendinyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-ol, 8-Chlor-5-cyclohexyl-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-ol,
- 8-Chlor-5-cyclohexioxy-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-ol,
 8-Chlor-5-(2-cyclohexenyl)-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-ol,
 8-Chlor-5-allyl-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-ol,
 9-Chlor-5-allyl-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-ol,
 - 8-Chlor-5-(2,2,2-trifluorethoxy)-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-ol, 8-Chlor-5-benzyloxy-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-ol,
- 6-Chlor-5-(phenethyloxy)-3-methyl-2,3,4.5-tetrahydro-1H-3-benzazepin-7-ol, 8-Chlor-5-(1-pyrroly)-3-methyl-2,3,4.5-tetrahydro-1H-3-benzazepin-7-ol, 8-Chlor-7-hydroxy-3-methyl-2,3,4.5-tetrahydro-spiro(1H-3-benzazepin-5,5-cyclopentan), 8-Chlor-7-lethoxy-formytoxy)-5-cyclohexyl-3-methyl-2,3,4.5-tetrahydro-1H-3-benzazepin,
 - 8-Chlor-7-(ethoxy-tormyloxy)-5-cytohoxyl-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin, 8-Chlor-7-(sopropyl-formyloxy)-5-allyl-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin, 8-Chlor-7-acetoxy-5-(3-methyl-2-butenyl)-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin,
- B-Chlor-T-(butoxy-methoxy)-5-allyl-3-methyl-2,34,5-fetahydro-1H-3-benzazepin und den pharmazeutisch annehmbaren Salzen der voranstehenden ausgewählt ist.
- 26 8. Verfahren zur Herstellung einer Verbindung der in Anspruch 1 angegebenen Formel I, welches ein Verfahren umfaßt, das aus den folgenden Verfahren A bis E ausgewählt ist:
 A: Reduktion einer Carbonylverbindung der allgemeinen Formel

B: Reduktion eines Esters der allgemeinen Formel

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C: Reduktion eines Salzes der allgemeinen Formel

an der Doppelbindung,

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intramolekulare Kondensation einer Verbindung der allgemeinen Formel

unter Eliminierung von HD und Bildung des Azepinnings, E: Reduktion einer Verbindung der allgemeinen Formet

an der olefinischen Doppelbindung,

wobei in den vorangehenden Formein die gepunkteite Linie im Azepinring eine wahlfreie Doppelbindung bedeutet, R¹, R², R³ R³ ander COOR³ ist, R³ in Anspruch 1 definient sind, R³ R³ oder COOR³ ist, R³ in Anspruch 1 definiertes R³ ist oder Alkowy ist (worin der Alkyfteit gerades oder verzweigtes Alkyf mit 1 bis 6 Kohlenstoffen ist), L³ ein Anion, vorzugsweise ein von einer Habgensäure oder einer Sulfornsäure stammendes Arion ist, D eine radskonstähige Gruppe ist, die unter Bildung des Azepinrings als DH eilminiert werden kann, und Z R³ oder R² ist,

- wobei das Verfahren nach Wunsch von einem oder mehreren der folgenden wahltreien Schritte gefolgt werden kann:
- (i) Entfernung etwaiger am Stickstoffatom befindlicher Schutzgruppen,
 (ii) Alkylierung am Stickstoffatom, wobei R³ Wasserstoff ist, unter Einführen von R³, das Alkyl ist,
- (iii) Veretherung oder Verthioetherung von R¹, wobei R¹ -OH ist und R² H ist, unter Ergeben eines entsprechenden Ethers oder Thiols,
- (iv) Veresterung von R⁵, wobei R⁵ -OH ist,
- (v) Halogenierung von R4, wobei R4 H ist,
- (vi) Hydroxymethylierung von R⁴, wobei R⁴ H ist, gefolgt von der Reduktion der auf diese Weise eingeführten Hydroxymethylgruppe zu Methyl,
- und vor oder nach dem wahlfreien Schritt oder den Schritten Entalkylierung von R^{4a}, wo R^{5a} Alkoxy ist, wobei die auf diese Weise erhaltene. Verbindung der Formel I in freier Form oder in Form eines oharmazeutisch annehmbaren Satzes isolen wird.

9. Verbindung der Formel II

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und die pharmazeutisch annehmbaren Salze derselben, worin

Q H, Halogen oder -OSO2R" bedeutet, worin R" CH2, CF3, Phenyl oder Tolyl ist,

R. H. grades oder verzweigtes Allyl mit 1 bis 8 Kohlenstörfatemen oder COR1* derstellt, worin R1* gerades oder verzweigtes Allyl mit 1 bis 6 Kohlenstörfatemen, Aryl, das eine unsubstituerte Dennychuppe ist, wobei aubstüherte Phenyl druch Allyl, Hydroxy, Alkoyx, Alkylthb, Halogen. Trifluermethyl oder deren Kombinationen mone- oder disubstühertes Phenyl tat, wobei substühertes Phenyl tat, wobei substühertes Phenyl durch Alkyl, Hydroxy, Alkoyx, Alkylthio, Halogen, Trifluermethyl oder deraph Kombinationen mone- oder der Alkyl Hydroxy, Alkoyx, Alkylthio, Halogen, Trifluermethyl oder deraph Kombinationen mone- oder disubstühertes Phenyl bedautet und der Alkylteil gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstöffenen ist) oder Halogeneilkyl fat, das gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstöffen ist, das mit 1 bis 5 Kohlenstöffen ist, das mit 1 bis 6 Kohlenstöffen ist

- R⁴ H, Halogen, gerades oder verzweigtes Alikyl mit 1 bis 8 Kohlenstoffelomen, Halogenalkyl, das gerades oder verzweigtes Alikyl mit 1 bis 6 Kohlenstoffen Ist, das mit 1 bis 5 Halogengruppen substitutent ist, oder Alikovyl sits (worin der Alikylteil gerades oder verzweigtes Alikyl mit 1 bis 8 Kohlenstoffatiomen ist).
 - R⁵⁶ -OR¹⁰, -N(R²)₂, -O-C(R²)₂ -OCOR¹³ oder Alkoxy darstellt (worin der Alkylteil gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstolfatomen ist), worin R⁷ H oder gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstolfatomen darstellt,
 - jeweils unabhlingig H, garades oder verzweigtes Alxyl mit 1 bis 6 Kohlenstoffatomen, Alxoy (worin der Altyleil garades oder verzweigtes Alxyl mit 1 bis 6 Kohlenstoffatomen, alxoy (Alxoyalxyl (worin beide Alixyleile gerades oder verzweigtes Alxyl mit 1 bis 6 Kohlenstoffatomen insid), Aralyl (worin der Ayrleil urusbetilteries oder substituleries Pennyl it on substituleries Phonyl durch Alkyl, Hydroy, Alkoya, Alkylhio, Halogen, Trifluormethyl oder deren Kombinationen mono- oder disubstituleries Pennyl bedustet, und der Alkyleil gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstoffatomen isty oder Aryl bedeutel, das eine nusbetiltuleries Phennyl durch kundr such mis substituleries Phennyl gudent, kundr substituleries Phennyl durch Alkyl, Hydroxy, Alkoya, Alkylhio, Halogen, Trifluormethyl oder deren Kombinationen mono- oder disubstituleries Phennyl bodeute.
- R10 H, -COR9 oder -CON(R9)2 bedeutet und
- R¹³ gerades oder verz-retigles Alkyl mit I bis 6 Kohlenstoffatomen, Aralkyl (worin der Arylfell unsubstitulerdes oder substitutierdes Phenryl lat (worin substitutierdes Phenryl durch Alkyl, Hydroxy, Alkory, Alkyfikh, haldgon, frilliumenthyl oder deren Kombinationen momo-oder disubstituierdes Phenryl bedeutel, das eine unsubstituierde oder substituierte Phenryl bedeutel, das eine unsubstituierde oder substituierte Phenryl gruppe ist (worin substituiertes Phenryl durch Alkyl, Hydroxy, Alkory, Alkyfithio, Haldgon, Trifluormethyl oder deren Kombinationen momo- oder disubstituiertes Phenryl bedeutel).
- so 10. Pharmazeutische Zusammensetzung, die als aktiven Bestandteil eine in einem der Ansprüche 1 bis 7 beanspruchte Verbindung zusammen mit einem pharmazeutisch annehmbaren Träger umfaßt.
- Verwendung einer in einem der Ansprüche 1 bis 7 beanspruchten Verbindung zur Herstellung einer pharmazeutischen Zusammensstzung zur Verwendung bei der Behandlung von Psychosen oder beunssion oder zum Bewirken von Andlossie, insbesondere zur Verwendung als Antipsychotikum.

Patentansprüche für folgenden Vertragsstaat : ES

1. Verfahren zur Herstellung einer Verbindung der Formel I

und deren pharmazeutisch annehmbarer Salze, worin:

-XR⁴, -CH₂R⁸, Cycloalkyl mit 3 bis 8 Kohlenstoffatomen, Cycloalkenyl mit 5 bis 8 Kohlenstoffatomen.

oder Pyrrolyl bedeutet,

R٩

- R² -H bedeutet oder R¹ und R² zusammen Alkandiyl bedeuten und eine zweiwertige, gerade oder verzweigte Kohlenwasserstoffkette mit 1 bis 6 Kohlenstoffatomen sind,
- R³ H oder gerades oder verzweigtes Allkyl mit 1 bis 6 Kohlenstolfatomen bedeutet, H, Halogen, gerades oder verzweigtes Allkyl mit 1 bis 6 Kohlenstolfatomen, Halogenalkyl, das gerades oder verzweigtes Allkyl mit 1 bis 6 Kohlenstolfatomen ist, welches mit 1 bis 5 Halogengruppen substitutient list, oder Alkoxy bedeutet (worin der Allyt)teil gerades oder
 - verzweigtes Alkyl mit 1 bis 6 Kohlenstoffatomen ist), -OR¹⁰, -N(R³)₂ oder -O·C(R⁷)₂ ·OCOR¹³ bedeutet,
 - H, gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstoffatomen, Cycloalkyl mit 3 bis 8 Kohlenstoffatomen, Cycloalkenyl mit 5 bis 8 Kohlenstoffatomen, Aralkyl (worin der Arviteil unsubstitulertes oder substituiertes Phenyl ist, worin substituiertes Phenyl durch Alkyl, Hydroxy, Alkoxy, Alkylthio, Halogen, Trifluormethyl oder deren Kombinationen mono- oder disubstituiertes Phenyl bedeutet, und der Alkylteil gerades oder verzweigtes Alkyl mit 1 bis 8 Kohlen-stoffatomen ist), Heteroarylalkyl (worin der Heteroarylteil eine aromatische heterocyclische Gruppe mit wenigstens einem O-, S- und/oder N-Atom ist und der Alkylteil gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstoffatomen ist), Halogenalkyl, das gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstoffen ist, das mit 1 bis 5 Halogengruppen substituiert lst, gerades oder verzweigtes Alkenyl mit 1 bis 6 Kohlenstoffatomen, Alkinyl mit 2 bis 6 Kohlenstoffatomen, Cycloalkylalkyl (wonn der Cycloalkylteil Cycloalkyl mit 3 bis 8 Kohlenstoffatomen ist und der Alkylteil gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstoffatomen ist), Cycloalkenylalkyl (worln der Cycloalkenylteil Cycloalkenyl mit 5 bis 8 Kohlenstoffatomen ist und der Alkylteil gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstoffatomen ist) oder Alkoxyalkyl (worin beide Alkylteile gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstoffatomen sind) bedeutet.
 - H doder gerades oder verzweigtes Allyf mit 1 bis 6 Kohlenstoffstomen bodeutet, Cyclasileyf mit 3 bis 8 Kohlenstoffstomen, Cyclasileyf mit 3 bis 8 Kohlenstoffstomen, Cyclasileyfallyf (worin der Cyclasilyfelli Cyclasileyf mit 3 bis 8 Kohlenstoffstomen ist und der Allyfelli gerades oder verzweigtes Allyf mit 1 bis 6 Kohlenstoffstomen ist) oder Cyclasilenylalityf (wobie der Cyclosilenyfielli Cyclasilenyf mit 3 bis 8 Kohlenstoffstomen ist) sturnd der Alkyfelli gerades oder verzweigtes Allyfi mit 1 bis 6 Kohlenstoffstomen ist sturnd der Alkyfelli gerades oder verzweigtes Allyfi mit 1 bis 6 Kohlenstoffstomen ist sturnd der Alkyfelli gerades oder verzweigtes Allyfi mit 1 bis 6 Kohlenstoffstomen ist sturnd der Alkyfelli gerades oder verzweigtes Allyfi mit 1 bis 6 Kohlenstoffstomen ist sturnd der Alkyfelli gerades oder verzweigtes Allyfi mit 1 bis 6 Kohlenstoffstomen ist sturnd der Alkyfelli gerades oder verzweigtes Allyfi mit 1 bis 6 Kohlenstoffstomen ist sturnd der Alkyfelli gerades oder verzweigtes Allyfi mit 1 bis 6 Kohlenstoffstomen ist sturnd der Alkyfelli gerades oder verzweigtes Allyfi mit 1 bis 6 Kohlenstoffstomen ist sturnd der Alkyfelli gerades oder verzweigtes Allyfi mit 1 bis 6 Kohlenstoffstomen ist sturnd der Alkyfelli gerades oder verzweigtes Allyfi mit 1 bis 6 Kohlenstoffstomen ist sturnd der Alkyfelli gerades oder verzweigtes Allyfi mit 1 bis 6 Kohlenstoffstomen ist sturnd der Alkyfelli gerades oder verzweigtes Allyfi mit 1 bis 6 Kohlenstoffstomen ist sturnd der Alkyfelli gerades oder verzweigtes Allyfi mit 3 bis 6 Kohlenstoffstomen ist sturnd der Alkyfelli gerades oder verzweigtes Allyfi mit 3 bis 6 Kohlenstoffstomen ist sturnd der Alkyfelli gerades oder verzweigtes Allyfi mit 3 bis 6 Kohlenstoffstomen ist sturnd der Alkyfelli gerades oder verzweigtes Allyfi mit 3 bis 6 Kohlenstoffstomen ist sturnd der Alkyfelli gerades oder verzweigtes Allyfi mit 3 bis 6 Kohlenstoffstomen ist sturnd der Alkyfelli gerades oder verzweigtes Allyfi mit 3 bis 6 Kohlenstoffstomen ist sturnd der Alkyfel
 - bedeutet, jeweils H. gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstoffatomen, Alkoxy (worin der Alkylteil gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstoffatomen Ist), Alkoxyalkyl (worin beide Alkylteile gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstoffatomen

sind), Arallyd (worin der Ayfteil unsubstituterles oder substitutierts Phenyl ist, worin substitutiertes Phenyl durch Ahyt, Hydroxy, Alkoxy, Altytitib, Haldgoen, Trilleurmehly) oder deren Kombinationen mon- oder disubstitutertes Phenyl bedeutet, und der Alkylteil gerades oder verzweigies Alkyl mit 1 bis 6 Kohlenstolitätomen ist) oder Ayri bedeutent, das eine unsubstitutierte oder substitutierte Phenylgruppe ist, wobei substitutierte Shenyl durch Alkyl, Hydroxy, Alkoxy, Alkythib, Haldgen, Trilleurmethyl oder deren Kombinationen mon- oder disubstitutierte Shenyl bedeutet,

R10 H, -COR9 oder -CON(R9)2 bedeutet,

gerades oder verzweigras Allyl mit 1 bis 6 Kohlenstoffatomen, Aralkyl (wor'n der Aryfteil unsubstitutieres oder substitutieres Pennyl I six obeits substitutieres Pennyl durch Allyl, Hydroxy, Alkoxy, Alkylibio, Halogen, Tiffliomresthyl oder deren Kombinationen monoder disubstitutieres Pennyl bedoeknut, und der Alkyliteit garades oder verzweigets Allyl, eini 1 bis 6 Kohlenstoffatomen ist) oder Aryf bedoektet, das eine unsubstitutiere oder substitutiere Pennyl rupche, alkyl, Hydroxy, Alkoxy, Alkylttio, Halogen, Tiffliomrethyl oder deren Kombinationen mono-oder disubstitutierts Pennyl rubce alkyl, Hydroxy, Alkoxy, Alkylttio, Halogen, Tiffliomrethyl oder deren Kombinationen mono-oder disubstitutierts

- -O- oder -S- bedeutet,
- m 0 oder 1 bedeutet,

R13

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- Y N oder CH bedeutet.
- Z CH₂ (falls Y nicht CH bedeutet) oder NR⁹ bedeutet und
- p und q jeweils unabhängig ganze Zahlen von 1 bis 3 bedeuten, sodaß die Summe von p plus q 1 bis 5 ist und p und g nicht beide 1 bedeuten, wenn Y N ist und Z NR³ ist,
- das ein Verlahren umfaßt, das aus den folgenden Verlahren A bis E ausgewählt ist:
 - A: Reduktion einer Carbonylverbindung der allgemeinen Formel

B: Reduktion eines Esters der allgemeinen Formel

C: Reduktion eines Salzes der allgemeinen Formel

an der Doppelbindung,

5

D: intramolekulare Kondensation einer Verbindung der allgemeinen Formel

unter Eliminierung von HD und Bildung des Azepinrings, Reduktion einer Verbindung der allgemeinen Formel

an der olefinischen Doppelbindung.

wobe in den vorangehenden Formein die gepunktete Linie im Azejnning eine wahlfreie Doppelbindung bedeutet, R1, P2, R1, R1 und R1³ vie in Auspruch 1 definient sind, R1³ R2 oder COOR1³ Ist, R1³ in Anspruch 1 definientes R1 ist oder Allowy ist (wonn der Alkyftell genedes oder verzweigtes Alkyf mit 1 bis 8 Köhlenstoffen ist), L2 ein Anion, vorzugsweise ein von einer Halogensäure oder einer Sulfonsäure stammendes Anion ist, D eine neständssfähige Gruppe ist, die unter Bildung des Azepinrings als OH eilmliniet werden kann, und Z R1 oder R2 ist, worden der R1 oder R2 ist, die unter Bildung des Azepinrings als OH eilmliniet werden kann, und Z R1 oder R2 ist, die unter Bildung des Azepinrings als OH eilmliniet werden kann, und Z R1 oder R2 ist, die unter mehrenen der folgenden wähltreien Schrifte gelichte.

- werden kann:
 - (i) Entfernung etwaiger am Stickstoffatom befindlicher Schutzgruppen,
 - (ii) Alkylierung am Stickstoffatom, wobei R3 Wasserstoff ist, unter Einführen von R3, das Alkyl ist,
 - (iii) Veretherung oder Verthioetherung von R1, wobei R1 -OH ist und R2 H ist, unter Ergeben eines
- entsprechenden Ethers oder Thiols, (iv) Veresterung von R⁵, wobei R⁵ -OH ist,
- (v) Halogenierung von R⁴, wobel R⁴ H ist,
- (vi) Hydroxymethyligrung von R*, wobei R* H ist, gefolgt von der Reduktion der euf diese Weise eingeführten Hydroxymethylgruppe zu Methyl,
- und vor oder nach dem wahlfrelen Schritt oder den Schritten Entalkylierung von R^{5a}, wo R^{5a} Alkoxy ist, wobei die auf diese Weise erhaltene Verbindung der Formel I in freier Form oder in Form eines pharmazeutisch annehmbaren Salzes Isoliert wird.
- 2. Verfahren gemaß Anspruch 1, wobei R¹-XFF, -Cht-R², Cycloalkyr mit 3 bis 8 Kohlenstoftstomen oder Cycloalkeryn mit 3 bis 8 Kohlenstoftstomen boder cycloalkeryn mit 3 bis 8 Kohlenstoftstomen kort verzweigtes Alkyl mit 1 bis 8 Kohlenstoftstomen, Cycloalkyr mit 3 bis 8 Kohlenstoftstomen, Aralkyrl (worin der Aryhleil unsubstituiertes oder substituiertes Phenryl ist und der Alkyhleil gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstoftstomen sit, hlabopendity, das gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstoftstomen sind, und refl Cycloalkyl mit 3 bis 8 Kohlenstoftstomen sind) und refl Cycloalkyl mit 3 bis 8 Kohlenstoftstomen, Cycloalkonyl mit 5 bis 8 Kohlenstoftstomen oder Alkywalkyl kondo bedaute.
- 3. Verfahren gemäß Anspruch 2, wobei R1 Cyclohexyl oder Cyclohexenyl bedeutet.

Verfahren gemäß Anspruch 2, wobei R¹

oder Pyrrolyl bedeutet, wo m 1 ist, und R³ H oder gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstoffatomen bedeutet.

- Verfahren gemäß einem der vorangehenden Ansprüche, worin R3 -CH3 bedeutet.
- 6. Verfahren gem
 ß einem der verangehenden Arepr
 üche, worin R^H Halogen, vorzugsweise Chlor, bedeutet und R^P-OH, COORP bedeutlut, wonin R^P gendes oder verzweigte schlor, bedeutet und R^P-OH, COORP bedeutlut, wonin R^P gendes oder verzweigte sklyd mit 1 bis 8 Knühenstoffstonnen Alkory (worin der Alkryfalle) gerades oder verzweigtes Alkryf mit 1 bis 6 Knühenstoffstonnen sind; bedeutet, R^P H bedeutet und R^D gerades oder verzweigtes Alkryf mit 1 bis 6 Knühenstoffstonnen bedeutet.
- 7. Verfahren gemäß Anspruch 1, wobei die hergestellte Verbindung aus
 - 8-Chlor-5-methoxy-3-methyl-2.3.4.5-tetrahydro-1H-3-benzazepin-7-ol.
 - 8-Chlor-5-ethoxy-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-ol,
 - 8-Chlor-5-ethylthio-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-ol,
- 7-Chlor-8-dimethylcarbamoyl-1-ethoxy-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin,
 - 8-Chlor-5-methyl-5-(1-piperidinyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-ol,
 - 8-Chlor-5-cyclohexyl-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-ol,
 - 8-Chlor-5-cyclohexjoxy-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-ol,
 - 8-Chlor-5-(2-cyclohexenyl)-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-ol,
- 8-Chlor-5-(2-cyclonexenyl)-3-methyl-2,3,4,5-tetranydro-1H-3-benzazepin-7-0 8-Chlor-5-allyl-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-0l,
- 8-Chlor-5-(2,2,2-trifluorethoxy)-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-ol,
 - 8-Chlor-5-benzyloxy-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-ol,
 - 8-Chlor-5-(phenethyloxy)-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-ol, 8-Chlor-5-(1-pyrrolyl)-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-ol,
 - 8-Chlor-7-hydroxy-3-methyl-2,3,4,5-tetrahydro-solrol 1H-3-benzazepin-5,5'-cyclopentan).
 - 8-Chlor-7-(ethoxy-formyloxy)-5-cyclchexyl-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin,
 - 8-Chlor-7-(isopropyl-formyloxy)-5-allyl-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin,
 - 8-Chlor-7-(methoxy-acetoxy)-5-allyl-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin,
- 8-Chlor-7-acetoxy-5-(3-methyl-2-butenyl)-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin,
- 8-Chlor-7-(I-butoxy-methoxy)-5-allyl-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin und den pharmazeutisch annehmbaren Salzen der voranstehenden ausgewählt ist.
 - 8. Verfahren zur Herstellung einer Verbindung der Formel II

und der pharmazeutisch annehmbaren Salze derselben, worin

- Q H, Halogen oder +OSO2R" bedeutet, worin R" CH3, CF3, Phenyl oder Tolyl ist,
 - H, gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstoffatomen oder COOR^{III} darstellit, worth R^{III} gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlensfoffatomen, Aryl, das eine unsubstituierte oder substituierte Phenylgruppe ist, wobei substituierte Phenyl durch Alkyl, Hydroxy, Alkoxy, Alkythib, Halooen, Triflipomethyl oder deren Kombinationen mono- oder

disubstituiertes Phenryl bedeutet, Aralbyl (evoint der Arytleil unsubstituiertes oder substituiertes Phenryl durch Albyl, Hydroxy, Alboxy, Albythio, Nalogon, Trifluormehyl oder deren Kombinationen mono- oder disubstituiertes Phenryl bodeutet, und der Allyteila gerades oder verzewigtes Albyl mit 1 bis 6 Kohlenstoftstemen ist) oder Halbgenanleyl sit, das gerades oder verzewigtes Albyl mit 1 bis 6 Kohlenstoften ist, das mit 1 bis 5 Halbgenanleyen autschlieften i St. 5 Halbgenanleyen autschl

- R⁴ H, Halogen, gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstoffatomen, Halogenalkyl, das gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstoffen ist, das mit 1 bis 5 Halogengruppen substituért ist, oder Alkoy ist (worin der Alkylteil gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstoffatomen ist).
- R^{5a} -OR¹⁰, -N(R³)₂, -O-C(R³)₂-OCOR¹³ oder Alkoxy darstellt (worin der Alky/teil gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstoftstomen ist), worin R⁷ H oder gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstoftstomen darstellt;
- ¹⁰ jeweils unabhängig H, gerades oder verzweigtes Abyr mit 1 bis 8 Kohlenstoftstomen, Abxory (vortion der Allysteils gerades oder verzweigtes Allyy mit 1 bis 6 Kohlenstoftstomen ist), Albxoyalbyt (wortin belied Abyrbeils gerades oder verzweigtes Abyr mit 1 bis 6 Kohlenstoftstomen ist), Albxoyalbyt (wortin belied Abyrbeils gerades oder verzweigtes Abyr mit 1 bis 6 Kohlenstoftsteinen ein eine Arghalle unsetsbeilderes oder subschliertes Phenyl beduett, und der Abfyrbeil gerades oder verzweigtes Albyr mit 1 bis 6 Kohlenstoftstomen ist) oder Aryl beduettel, das eine unsetsbellierte oder subschlierter Phenyl petroduct, und der Abfyrbeil gerades oder verzweigtes Albyr mit 1 bis 6 Kohlenstoftstomen ist) oder Aryl beduettel, das eine unsetsbellierte oder subschlierter Phenyl gerades; two ein subschliertes Phenyl durch Albyr, Hydroxy, Albxoy, Allythio, Halogen, Trifluormethyl oder deren Kombinstonen mono- oder disabsfiliertes Phenyl beduetters Phenyl durch Albyr,
- R10 H. -COR3 oder -CON(R3) bedeutet und
- R¹³ gerades oder verzweigtes Alkyl mit 1 bis 8 Kohlenstoffatomen, Aralkyl (worin der Arylteil unsubstituiertes Deber substituiertes Phenyl tist (worin substituiertes Phenyl durch Alkyl, Hydroxy, Alkylthic, Malegen, Trifilormenthyl oder deen Kohminationen monto-oder disubstituiertes Phenyl bedeutet) und der Alkylteil gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstörfatomen sit) oder Aryl bedeutet, das eine unsubstituierte oder substituierte Phenyl grupe ist (worin substituiertes Phenyl durch Alkyl, Hydroxy, Alkory, Alkylthio, Halogen, Trifilormenthyl oder deen Kohminationen mon-oder disubstituiertes Phenyl bedeutet,

welches das Halogenieren der Verbindung der Formel VIII

VIII

unter Herstellen einer Verbindung der Formel II, worin Q Halogen bedautet, und die nachfolgende Hydrolysierung zu einer OH-Gruppe und Reaktion mit einem Sulfernybalogenid oder -anhydrid unter Herstellen einer Verbindung der Formel II umfaßt, worin Q -OSQ-R* ist.

 Verfahren zum Herstellen einer pharmazeutischen Zusammensetzung, welches das Mischen einer gemäß einem der Ansprüche 1 bis 7 hergestellten Verbindung als aktivem Bestandteil mit einem pharmazeutisch annehmbaren Träger umfaßt.

Patentansprüche für folgenden Vertragsstaat : GR

1. Verbindung mit der Strukturformel I

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D6

R^g

und die pharmazeutisch annehmbaren Salze derselben, worin:

R¹ -XR⁶, -CH₂R⁸, Cycloalkyl mit 3 bis 8 Kohlenstoffatomen, Cycloalkenyl mit 5 bis 8 Kohlenstoffatomen,

oder Pyrrolyl bedeutet,

R² -H bedeutet oder R¹ und R² zusammen Alkandlyl bedeuten und eine zweiwertige, gerade oder verzweigte Kohlenwasserstoffkette mit 1 bis 6 Kohlenstoffatomen sind,

H oder gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstoftstomen bedeutet, H, Halogen, gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstoftstomen, Halogenalkyl, das gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstoftstomen ist, welches mit 1 bis 5 Halogengruppen substitutient ist, oder Alkoxy bedeutet (worin der Alkylat gerades oder

verzweigtes Alkyl mit 1 bis 6 Kohlenstoffatomen ist), -OR¹⁰, -N(R³)₂ oder -O·C(R⁷)₂·OCOR¹³ bedeutet,

H. gerades oder verzweigtes Alkyl mit 1 bls 6 Kohlenstoffatomen, Cycloalkyl mit 3 bis 8 Kohlenstoffatomen, Cycloalkenyl mit 5 bis 8 Kohlenstoffatomen, Aralkyl (worin der Arviteil unsubstitulertes oder substituiertes Phenyl ist, worin substituiertes Phenyl durch Alkyl, Hydroxy, Alkoxy, Alkylthio, Halogen, Trifluormethyl oder deren Kombinationen mono- oder disubstituiertes Phenyl bedeutet, und der Alkylteil gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstoffatomen ist), Heteroarylalkyl (wonn der Heteroarylteil eine aromatische heterocyclische Gruppe mit wenigstens einem O-, S- und/oder N-Atom ist und der Alkylteil gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstoffatomen ist), Halogenelkyl, das gerades oder verzweigtes Alkyl mit 1 bis 8 Kohlenstoffen ist, das mit 1 bis 5 Halogengruppen substituiert ist, gerades oder verzweigtes Alkenyl mit 1 bis 6 Kohlenstoffatomen, Alkinyl mit 2 bis 6 Kohlenstoffatomen, Cycloalkylalkyl (worin der Cycloalkylteil Cycloalkyl mit 3 bis 8 Kohlenstoffatomen ist und der Alkylteil gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstoffatomen ist), Cycloalkenylalkyl (worin der Cycloalkenylteil Cycloalkenyl mit 5 bis 8 Kohlenstoffatomen ist und der Alkylteil gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstoffatomen ist) oder Alkoxvalkyl (worin beide Alkylteile gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstoffatomen sind) bedeutet.

H oder gurades oder verzweigige Allyr mit 1 bis 6 Kohlenstofitatomen bedeutet, Cycloalityr imt 3 bis 8 Kohlenstofitatomen, Cycloalkonyr mit 5 bis 8 Kohlenstofitatomen, Cycloalkyrialityr (morin der Cycloalityr mit 3 bis 8 Kohlenstofitatomen; sit und der Allyfleit gerades oder verzweigiges Allyr mit 1 bis 6 Kohlenstofitatomen ist) uder Cycloalkonyralityr (Morbie Cycloalkonyrimt 15 bis 6 Kohlenstofitatomen ist und der Allsytteil gerades oder verzweigtes Allyr mit 1 bis 6 Kohlenstofitatomen bedeutset.

jeweils H, gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstoffatomen, Alkoxy (worin der Alkylteil gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstoffatomen ist), Alkoxystel (worin beide Alkylteile eardes) oder verzweidtes Alkyl mit 1 bis 6 Kohlenstoffatomen

sind), Arallyl (worin der Ayrlieil unsubstitutiertes oder substitutiertes Phonyl ist, worin substitutiertes Phonyl durch Allyl, Hydroxy, Altoxy, Allythio, Haldgon, Trifluormethyl oder deren Kombinationen mone- oder disubstitutiertes Phonyl bedeutet, und der Allyleil gerades oder verzweigtes Allyl mit in bis 6 Kohlessoritationen ist oder Ayrlbeduren, das eine unsubstitutierte oder substitutierte Phonylgruppe ist, wobei substitutiertes Phonyl durch Allyl, Hydroxy, Alloxy, Altythio, Haldgen, Trifluormethyl oder deren Kombinationen mone oder disubstitutiertes Phonyl bedeutet,

R¹⁰ H, -COR³ oder -CON(R³)₂ bedeutet, R¹³ gerades oder verzweigtes Alkyl mit 1

gerades oder verzweigtes Altyl mit 1 bis 6 Kohlenstoffatomen, Aralkyl (worin der Arylteil unsübsthieries oder substitueries Phenyl ist, wobei substitueries Phenyl durch Altyl, Hydroxy, Alkoxy, Altyttiko, Halegon, Triffbormethyl oder deren Kombnistonen monoder disubstitueries Phenyl bedeutet, und der Altytteil gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstoffatomen ist) oder Aryl bedeutet, das eine unsubstitueries der substitutierie Phenyl gruppe ist, wobei substitutiers Phenyl durch Altyl, Hydroxy, Alkoxy, Altyttiko, Halogen, Triffbormethyl oder deren Kombinationen mono- oder disubstitulertes Phenvi bedautet.

- -O- oder -S- bedeutet.
- m 0 oder 1 bedeutet,

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z

- Y N oder CH bedeutet,
 - CH₂ (falls Y nicht CH bedeutet) oder NR⁹ bedeutet und
- p und q jeweils unabhängig ganze Zahlen von 1 bis 3 bedeuten, sodaß die Summe von p plus q 1 bis 5 ist und p und q nicht beide 1 bedeuten, wenn Y N ist und Z NR⁵ ist.
- 2. Verbindung gemäß Anspruch 1, worin R¹-XFF, -CH₂R², Cyclosikyr mit 3 bis 8 Kohlenstörfatornen oder Cyclosikeryr mit 5 bis 8 Kohlenstörfatornen besetnet, worin X -O oder S- bedeute, R² Gerades oder verzweiges Alkyl mit 1 bis 8 Kohlenstörfatornen, Cyclosikyr mit 3 bis 8 Kohlenstörfatornen, Aralkyl (worin der Arytiell unsubstiluiertes oder substitutertes Phenryl ist und der Alkytiell gerades oder verzweiges Alkyl mit 1 bis 6 Kohlenstörfatornen ist, Halsgomankyl, das gerades oder verzweiges Alkyl mit 1 bis 6 Kohlenstörfatornen sind, but 6 Kohlenstörfatornen sind) und f² Cyclosikyr mit 3 bis 8 Kohlenstörfatornen, Cyclosikoryl mit 5 bis 8 Kohlenstörfatornen sind) und f² Cyclosikyr mit 3 bis 8 Kohlenstörfatornen oder Alkytelle gerades oder verzweigliss Alkyl mit 1 bis 6 Kohlenstörfatornen sind) bedeuten.
- 3. Verbindung gemäß Anspruch 2, worin R1 Cyclohexyl oder Cyclohexenyl bedeutet.
- 4. Verbindung gemäß Anspruch 1, worin R1

oder Pyrrolyl bedeutet, wo m 1 ist, und R⁵ H oder gerades oder verzweigtes Alkyl mit 1 bis 8 Kohlenstoffalomen bedeutet.

- 5. Verbindung gemäß einem der vorangehenden Ansprüche, worin R3 -CH₃ bedeutet.
- 6. Verbindung gemäß einem der vorangehenden Ansprüche, worin R¹¹ Halogen, vorzugsweise Chlor, beduetst und R² Och God-Po-Ger Po-Ger Po-
- Verbindung gemäß Anspruch 1, wobei die Verbindung aus 8-Chlor-5-methoxy-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-ol, 8-Chlor-5-ethoxy-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-ol,

8-Chlor-5-ethylthio-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-ol,

7-Chlor-8-dimethylcarbamoyl-1-ethoxy-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin, 8-Chlor-3-methyl-5-(1-piperidinyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-ol,

8-Chlor-5-cyclohexyl-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-ol,

8-Chlor-5-cyclohexloxy-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-ol, 8-Chlor-5-(2-cyclohexenyl)-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-ol,

8-Chlor-5-allyl-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-ol,

8-Chlor-5-(2,2,2-trifluorethoxy)-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-ol.

8-Chlor-5-benzyloxy-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-ol,

8-Chlor-5-(phenethyloxy)-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-ol, 10

8-Chlor-5-(1-pyrrolyl)-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-ol,

8-Chlor-7-hydroxy-3-methyl-2,3,4,5-tetrahydro-spiro[1H-3-benzazepin-5,5'-cyclopentan], 8-Chlor-7-(ethoxy-formyloxy)-5-cyclohexyl-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin,

8-Chlor-7-(isopropyl-formyloxy)-5-allyl-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin, 8-Chlor-7-(methoxy-acetoxy)-5-allyl-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin,

8-Chlor-7-acetoxy-5-(3-methyl-2-butenyl)-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin,

8-Chlor-7-(t-butoxy-methoxy)-5-allyl-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin und den pharmazeutisch annehmbaren Salzen der voranstehenden ausgewählt ist.

- 20 8. Verfahren zur Herstellung einer Verbindung der in Anspruch 1 angegebenen Formel I, welches ein Verfahren umfaßt, das aus den folgenden Verfahren A bis E ausgewählt ist:
 - A: Reduktion einer Carbonylverbindung der allgemeinen Formel

Reduktion eines Esters der allgemeinen Formel

Reduktion eines Salzes der allgemeinen Formel

- an der Doppelbindung.
- D: intramolekulare Kondensation einer Verbindung der allgemeinen Formel

unter Eliminierung von HD und Bildung des Azepinrings, Reduktion einer Verbindung der allgemeinen Formet

an der olefinischen Doppelbindung,

- wobei in den vorangehenden Formeln die gepunktete Linie im Azepinring eine wahlfreie Doppelbindung. bedeutet, R1, R2, R3, R4 und R13 wie in Anspruch 1 definiert sind, R3a R3 oder COOR13 ist, R5a in Anspruch 1 definiertes R5 ist oder Alkoxy ist (worin der Alkylteil gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstoffen ist), L3 ein Anion, vorzugsweise ein von einer Halogensäure oder einer Sulfonsäure stammendes Anion ist. D eine reaktionsfähige Gruppe Ist, die unter Bildung des Azepinrings als DH eliminiert werden kann, und Z R1 oder R2 Ist,
- wobei das Verfahren nach Wunsch von einem oder mehreren der folgenden wahlfreien Schritte gefolgt werden kann:
 - Entfemung etwaiger am Stickstoffatom befindlicher Schutzgruppen.
 - (ii) Alkylierung am Stickstoffatom, wobei R3 Wasserstoff ist, unter Einführen von R3, das Alkyl Ist, (iii) Veretherung oder Verthioetherung von R1, wobei R1 -OH Ist und R2 H ist, unter Ergeben eines
 - entsprechenden Ethers oder Thiols, (iv) Veresterung von R5, wobel R5 -OH Ist,

 - (v) Halogenierung von R4, wobei R4 H ist, (vi) Hydroxymethylierung von R⁴, wobei R⁴ H ist, gefolgt von der Reduktion der auf diese Welse
- eingeführten Hydroxymethylgruppe zu Methyl. und vor oder nach dem wahlfreien Schritt oder den Schritten Entalkylierung von R5e, wobel R5e Alkoxy
 - wobei die auf diese Welse erhaltene Verbindung der Formel I in freier Form oder in der Form eines pharmazeutisch annehmbaren Salzes isoliert wird.
- 45 9. Verbindung der Formel II

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und die pharmazeutisch annehmbaren Salze derselben, worin

- H, Halogen oder -OSO₂R" bedeutet, worin R" CH₃, CF₃, Phenyl oder Tolyl ist,
- H. gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstoffatomen oder COOR14 darstellt, worin R16 gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstoffatomen, Aryl, das eine unsubstituierte oder substituierte Phenylgruppe Ist, wobei substituiertes Phenyl durch Alkyl,

Hydroxy, Alkoxy, Alkythio, Halogen, Trifluormethyl oder deren Kombinationen mon-o oder dissubstituiertes Penenyi bedeutes, Haliq (verni der Ayleile mususbituiertes Secte substituiertes Phenyl ist, wobei substituiertes Phenyl durch Alkyl, Hydroxy, Alkoxy, Alkythio, Halogen, Trifluormethyl oder deren Kombinationen mon-o oder disubstituiertes Phenyl bedeutet, und der Alkyteil gerades oder verzweigies Alkyl mit 1 bis 6 Kohlenstofatomen ist) oder Halogenalkyl ist, das gerades oder verzweigies Alkyl mit 1 bis 6 Kohlenstoften ist, das mit 1 bis 5 Halogenquopen substituieri lab.

- R¹ H, Halogen, gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstoffatomen, Halogenalkyl, das gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstoffen ist, das mit 1 bis 5 Halogengruppen substituiert ist, oder Alkoxy ist (worin der Alkylteil gerades oder verzweigtes Alkyl mit 1 bis 6 Kohlenstoffatomen ist).
- R^{5a} OR¹⁰, -N(R²)_b, O-C(R²)_b-OCOR¹³ oder Alkoxy darstellt (worin der Alkytheil gerades oder verzweigtes Alkyt mit 1 bis 6 Kohlenstoffatomen ist), worin R² H oder gerades oder verzweigtes Alkyt mit 1 bis 6 Kohlenstoffatomen darstellt,
- Pt² jewells unabhängig H, gerades oder verzweigtes Aflyd mit 1 bis 6 Kohlenssoftatomes, Aktoxy (veröni der Alkyfeldi gerades oder verzweigtes Aflyd mit 1 bis 6 Kohlenssoftatome ist), Alkoxyalkyl (wordin beide Alkyfelle gerades oder verzweigtes Allyd mit 1 bis 6 Kohlenssoftatome sind), Aralleyd (wordin beide Alkyfelle gerades oder verzweigtes Allyd mit 1 bis 6 Kohlenssoftatome sind), Aralleyd kowni der Aryletide unsachtlicherends oder substitutiers Phenyl durch Alkyf. Hydroxy, Alkoyy Alkyfthio, Halogen, Trifluormethyl oder deren Kombinationen mono- oder dissolutieuters Phenyl bedeutet, und der Alkyfelli gerades oder verzweigtes Alkyf mit 1 bis 6 Kohlenssoftatomen ist) oder Anyl bedeutet, das eine unsubstitutiers betwei substitutiere bereydruppes jett vomet abstitutieren Serven judich substitutieren Serven judich party gruppe ist, vomet abstitutieren Serven judich serven
 - R10 H, -COR9 oder -CON(R9)2 bedeutet und
 - gerades oder verzweigtes Asyl mit 1 bis 6 Kohlenstoffatomen, Arallyd (worin der Arylfeil unsubstituieres Oder substituieres Perenyl ist vorin substituieres Perenyl sit vorin substituieres Perenyl durch Alkyl, Hydroxy, Alkoxy, Alkylthie, Halogen, Trifluomethyl oder deren Kombinationen mono-oder disubstituieres Phenyl bedeuted, tas eine unsubstituiere der substituiere Rohlenstraffatomen sit) oder Aylb bedeuted, das eine unsubstituiere der substituiere Phenyl-gruppe ist (worin substituieres Phenyl bedeuted, tas einer einsubstituieres Alkyl, Hydroxy, Alkoxy, Alkylthio, Halogen, Trifluomethyl oder deren Kombinationen mono- oder disubstituieries Phenyl bedeutet).
- Verfahren zum Herstellen einer pharmazeutischen Zusammensetzung, welches das Mischen einer gemäß einem der Ansprüche 1 bis 7 hergestellten Verbindung als aktivem Bestandteil mit einem pharmazeutisch annehmhären Träger unfallst.
- 11. Verwendung einer In einem der Ansprüche 1 bis 7 beanspruchten Verbindung zur Herstellung einer pharmazeutschen Zusammensatzung zur Verwendung bei der Behandtung von Psychosen oder Depression oder zum Berwirken von Analgesie, insbesondere zur Verwendung als Antibyschotikum.

Revendication

Revendications pour les Etats contractants sulvants : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

45 1. Composé ayant la formule de structure !

$$R^4$$
 R^5
 R^1
 R^2

et ses sels acceptables en pharmacie, où :

R¹ représente -XR⁵, -CH₂R³, cycloalkyle ayant 3 à 8 atomes de carbone, cycloalcényle ayant 5 à 6 atomes de carbone,

$$-(CH_2)_{m}C=C$$
 R^9
 $(CH_2)_p$
 $CCH_2)_q$
 $CCH_2)_q$

ou pýrrolyle ;

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R² représente -H ou bien R¹ et R² représentent ensemble alcanediyle étant une chaîne d'hydrocarbure divalent, droite ou ramifiée ayant 1 à 6 atomes de carbone;

R3 représente H ou un alkyle droit ou ramifié ayant 1 à 6 atomes de carbone ;

R¹ représente H, halo, alivyle droit ou ramifié ayant 1 à 6 atomes de carbone, haloalkyle étant un alkyle droit ou ramifié ayant 1 à 6 atomes de carbone susbitué par 1 à 5 groupes halo ou bien alcoxy (où la portion alkyle est un alkyle droit ou ramifié ayant 1 à 6 atomes de carbone);

R5 représente -OR10, -N(R3 b ou -O.C(R7 b.OCOR13 :

In represented M. altyle droit our samilé ayant 1 à 8 atomes de carbone, cyclosidyle ayant 3 à 8.

Fri représente M. altyle droit our samilé ayant 1 à 8 atomes de carbone, arailyle (où la portion ayrè est un phényle non substitué ou abstitué où la phényle non substitué our abstitué our abstitué our abstitué our autorité de la phényle non substitué our autorité de la partie altyle de colt ou ramifé de sant la grant 1 à 8 atomes de carbone, logic partie altyle de la partie altyle de sun altyle droit ou ramifé ayant 1 à 8 atomes de carbone, logic partie altyle de la partie altyle de sun altyle droit ou ramifé ayant 1 à 8 atomes de carbone, out bien alconyaltyle (où la portien altyle set un altyle droit ou ramifé ayant 1 à 8 atomes de carbone, out bien alconyaltyle (où la portien altyle set un altyle droit ou ramifé ayant 1 à 8 atomes de carbone et un altyle droit ou ramifé ayant 1 à 8 atomes de carbone et un altyle droit ou ramifé ayant 1 à 8 atomes de carbone et un altyle droit ou ramifé ayant 1 à 8 atomes de carbone et un altyle droit ou ramifé ayant 1 à 8 atomes de carbone et un altyle droit ou ramifé ayant 1 à 8 atomes de carbone et un altyle droit ou ramifé ayant 1 à 8 atomes de carbone et un altyle droit ou ramifé ayant 1 à 8 atomes de carbone et un altyle droit ou ramifé ayant 1 à 8 atomes de carbone et un altyle droit ou ramifé ayant 1 à 8 atomes de carbone et un

R7 représente H ou blen alkyle droit ou ramifié ayant 1 à 6 atomes de carbone ;

Rº représente cyclosityle ayant 3 à 8 atomes de carbone, cyclositényle ayant 5 à 8 atomes de carbone, cyclositylatiyle (où la portion cyclosityle est un cyclosityle ayant 3 à 6 atomes de carbone et la portion altyle est un altyle droit ou ramillé ayant 1 à 6 atomes de carbone) ou cyclositénylatiyle (où la portion de cyclositényle est un cyclositényle ayant 5 à 8 atomes de carbone et la portion d'altyle set un altyle droit ou ramillé ayant 1 à 6 atomes de carbone);

Chaque RT représente indépendamment It, alixyle droit ou ramifié ayant 1 à 8 atomes de carbone, alcony (oi la portion alixyle est un alixyle droit ou ramifié ayant 1 à 6 atomes de carbone, alconyalixyle (où les deux portions alixyles sont des alixyles droits ou ramifiés ayant 1 à 6 atomes de carbone, aralixyle (où la portion arvive est un phényle non substitué où les phényle substitué profesente un phényle monco- ou d'substitué par a ralixyle, hydrova, aloxyon, alixythin, lain, trittucométhyle ou leurs associations et la portion d'alixyle est un alixyle droit ou ramifié ayant 1 à 6 atomes de actionojeu bien aryle étant un groupe phényle non substitué ou substitué du le phényle substitué représente un phényle monco- ou di-substitué par alixyle, hydroxy, alcoxy, alixythio, halo, trifluorométhyle ou leurs associations :

R10 représente H. -COR9 ou -CON(R9):

R13 représente alkyle droit ou ramifié ayant 1 à 6 atomes de carbone, aralkyle (où la portion d'aryle est un piényle nos usbituté ou substituté où la priényle substituté représents phényle monc- ou disubstituté par alkyle, hydrova, alcoux, alcythio, hab, chilliconnétifyle ou beurs associations et la portion d'alkyle est un alkyle droit ou ramifié ayant 1 à 6 atomes de carbone) ou bien aryle étant un groupe phényle non substituté ou substituté où la prényle substituté représente phényl monc ou di-substituté par akyle, hydrova, docvy, alkylithio, hab, utiliuroométhyle ou leurs associations ;

X représente -O- ou -S; m représente O ou 1:

Y recrésente N ou CH :

Z représente CH2 (si Y ne représente pas CH) ou bien NR9 ; et

chacun de p et q représente indépendamment des nombres entiers de 1 à 3 tets que la somme de p plus q soit comprise entre 1 et 5 et que p et q ne représentent pas tous deux 1 quand Y est N et que Z est NP?

- 3 2. Composé solon la revandication 1 où R1 représente XRF, C-CheRP, cycloaltyle ayant 3 à 8 atomes de carbone ou cycloaltérije ayant 5 à 8 atomes de carbone, cycloaltyle ayant 3 à 8 atomes de carbone un alkyle droit ou ramifié ayant 1 à 8 atomes de carbone, cycloaltyle ayant 3 à 8 atomes de carbone, aratiyle (où la proficin aryle est un phéryle non substitué ou substitué et la portion alkyle et ort un alkyle droit ou ramifié ayant 1 à 6 atomes de carbone, habalsiyle étant un alkyle droit ou ramifié ayant 1 à 6 stomes de carbone alkyle droit ou ramifié ayant 1 à 6 groupes habo ou alcoys alkyle (ol) les deux portions d'alkyle sont des sikyles droits ou ramifié ayant 1 à 6 atomes de carbone et l'i représente cycloaltyle ayant 3 à 8 atomes de carbone cycloaltyle ayant 5 à 8 atomes de carbone cycloaltyle (ol) les deux options d'alkyles droits ou artifiés ayant 1 à 6 atomes de carbone.
- 15 3. Composé selon la revendication 2 où R1 représente cyclohexyle ou cyclohexényle.
 - 4. Composé selon la revendication 1, où R1 représente



ou pyrrolyle où m est 1 et R9 représente H, ou bien alkyle droit ou ramifié ayant 1 à 6 atomes de carbone.

- 30 5. Composé salon l'une quelconque des revendications précédentes où R3 représente -CH3.
 - 6. Composé soion l'une quiebonque des revendications précédentes où Pri représente haib, de préférence chiore et R° profésente On A-OCDR ° u. O-(CPR) p. OCDR ° u. O-(CPR) p. O-(CPR) p. OCDR ° u. O-(CPR) p. O-(
- 7. Composé selon la revendication 1, ledit composé étant choisi parmi :
 - 8-Chlor-5-méthoxy-3-méthyl-2,3,4,5-tétrahydro-1H-3-benzazépine-7-ol,
 - 8-Chlor-5-éthoxy-3-méthyl-2,3,4,5-tétrahydro-1H-3-benzazépine-7-of,
 - 8-Chloro-5-éthylthio-3-méthyl-2,3,4,5-tétrahydro-1H-3-benzazépine-7-ol,
 - 7-Chloro-8-diméthylcarbamoyl-1-éthoxy-méthyl-2,3,4,5-tétrahydro-1H-3-benzazépine,
- 8-chloro-3-méthyl-5-(t-pipéridinyl)-2,3,4,5-tétrahydro-1H-3-benzazépine-7-ol, 8-chloro-5-cyclohexyl-3-méthyl-2,3,4,5-tétrahydro-1H-3-benzazépine-7-ol,
- 8-chloro-5-cyclohexyloxy-3-méthyl-2,3,4,5-tétrahydro-1H-3-benzazépine-7-ol,
 - 8-Chloro-5-(2-cyclohexényl)-3-méthyl-2,3,4,5-tétrahydro-t H-3-benzazépine-7-ol,
- 8-chloro-5-allyl-3-méthyl-2,3,4,5-tétrahydro-1H-3-benzazépine-7-ol,
- 8-chloro-5-(2,2,2-trifluoroéthoxy)-3-méthyl-2,3,4,5-tétrahydro-1H-3-benzazépine-7-ol, 8-Chloro-5-benzyloxy-3-méthyl-2,3,4,5-tétrahydro-1H-3-benzazépine-7-ol,
- 8-chloro-5-(phénéthyloxy)-3-méthyl-2,3,4,5-tétrahydro-t H-3-benzazépine-7-ol,
 - 8-chloro-5-(t-pyrrolyl)-3-méthyl-2,3,4,5-tétrahydro-1H-3-benzazépine-7-ol,
- 8-chloro-7-hydroxy-3-méthyl-2,3,4,5-tétrahydro-spiro [1H-3-benzazépine-5,5'-cyclopentane], 8-chloro-7-(éthoxy-formyloxy)-5-cyclohexyl-3-méthyl-2,3,4,5-tétrahydro-1H-3-benzazépine,
- 8-Chloro-7-(isopropyl-formyloxy)-5-allyl-3-méthyl-2,3,4,5-tétrahydro-1H-3-benzazépine,
 - 8-chloro-7-(méthoxy-acétoxy)-5-allyl-3-méthyl-2,3,4,5-tétrahydro-1H-3-benzazépine,
 - 8-Chloro-7-acétoxy-5-(3-méthyl-2-butényl)-3-méthyl-2,3,4,5-tétrahydro-1H-3-benzazépine,
 - 8-chloro-7-(t-butyroxy-méthoxy)-5-allyl-3-méthyl-2,3,4,5-tétrahydro-1H-3-benzazépine,

- et les sels acceptables en pharmacie de ce qui précède.
- 8. Procédé pour la préparation d'un composé de la formule I selon la revendication 1, lequel procédé comprend un procédé choisi par les procédés A à E qui suivent :
 - A : réduction d'un composé carbonyle de la formule générale :

B. réduction d'un ester de la formule générale :

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C : réduction de la double liaison d'un sel de la formule générale :

D : condensation intramoléculaire d'un composé de la formule générale :

avec élimination de HD et formation du noyau d'azépine,

E : réduction à la double liaison oléfinique, d'un composé de la formule générale :

où, dans les formules ci-dessus, la ligne en pointillé dans le noyau d'azgine représente une double liaion facultative, R. P. R. P. et pl.º sou fus ieu desfinis à la revendication 1, P. est et P. ou COOR¹, P. est P. let que défini à la revendication 1 ou est alcory (où la portion d'allyte est un allyte de control ou armitif ayant 1 à 8 stores de carbone). Le set un ainoi, de préférence un ainoi definé d'un facile sutionique, D est un groupe réactif pouvent être éliminé en tant que DH avec termition du noveu d'abscine at c. et R ou P. P.

ledit procédé étant suivi, si on le souhaite, par une ou plusieurs des étapes facultatives suivantes :

- (i) élimination de tout groupe protecteur présent à l'atome d'azote,
 (ii) alkytation à l'atome d'azote où R₂ est hydrogène pour introduire R³ qui est alkyle,
 - (ii) éthérification ou thioéthérification de R¹ où R¹ est •OH et R² est H pour donner un éther ou thiol
 - correspondent,
 - (iv) estérification de R5 où R5 est -OH,
- (v) halogénation de R* où R* est H .
 - (vi) hydroxyméthylation de R⁴ où R⁴ est H, avec ensuite réduction du groupe hydroxyméthyle ainsi introduit en méthyle.
 - et avant ou après ladite ou lesdites étapes facultatives, désalkylation de R5º où R5º est alcoxy,
- le composé ainsi obtenu de formule I étant isolé sous forme libre ou bien sous la forme d'un sel acceptable en pharmacie.

9. Composé de la formule II

et ses sels acceptables en pharmacie, où :

Q représente H, halo ou -SO₂R" où R" est CH₃, CF₃, phényle ou tolyle ;

R¹² représente H, airyle droit ou ramifé ayent 1 à 8 stomes de cathone ou COOR¹⁴ où R¹⁴ est alityle droit ou ramifé ayent 1 à 6 stomes de cathone, anyle featur un groupe phényle non bustistée ou substitué du phényle substitué représente phényle mono- ou d'aubstitué par alityle, hydroxy, aboxy, alitythic, hab, rithurométhyle ou leura associations, arallyle (ou la portion d'aryle est un pényle nonsubstitué ou substitué où le phényle substitué représente phényle mono-ou d'substitué par alityle, hydroxy, aboxy, alitylifiho, haba, triflicomorféthyle ou leura sosociations et la portion d'aivly est un alityle droit ou ramifé ayent 1 à 8 atomes de cathone) ou habatkyle, étant un alityle droit ou ramifé ayent 1 à 8 dromes de cathone) ou habatkyle, étant un alityle droit ou ramifé ayent 1 à 8 dromes de cathone substitué par 1 à 8 proupes habe.

R* représente H, halo, alkyte droit ou ramifié ayant 1 à 8 atomes de carbone, haloalkyte étant un alkyte droit ou ramifié ayant 1 à 8 atomes de carbone substitué par 1 à 5 groupes halo ou bien alcoxy (où la portion d'alkyte est un alkyte fortie ou ramifié ayant 1 à 6 atomes de carbone);

R^{2a} représente -OR^{1o}, -N(R²)_b, -O.C(R²)_b, OCOR¹³ ou atcoxy (où la portion alkyle est un alkyle droit ou ramifié ayant 1 à 8 atomes de carbone) ; où R² représente H, ou un alkyle droit ou ramifié ayant 1 à 6 atomes de carbone :

chaque Pt représente Indépendamment H, un altyle droit ou ramilié ayant 1 à 6 atomes de carbone, alcony (où la portion d'allyle set un altyle droit ou ramilié ayant 1 à 6 atomes de carbone) a alconyaltyle (où les deux portions d'altyle sont des altyles droits ou ramiliés ayant 1 à 6 atomes de carbone), arallyle (où la portion d'arrije est un pirkerije enn substituit do substituit do la phinyle substituit représente phinyle mono- ou di-aubstituit par altyle, hydroxy, alcony, altylthio, habi, nittiourométhyle ou leura sessociations et la portion d'attivje est un altyley de crit ou ramilié syant 1 à 6 atomes de carbone) ou aryle feant un groupe phényle non substituit ou substituit représente phényle mono- ou d'eusstituit par altyle, hydroxy, alcoxy, skirythio, habi, intilionométhyle ou leura sessociations,

R10 représente H. -COR3 ou -CON(R3): et

R¹³ représents altyle droft ou ramifé ayant 1 à 6 atomes de carbone, analyte (où la portion d'aryle set un plénife non substitué ou ba plénife substitué représents un plénife non-ou disubstitué par altyle, hydroux, alcoxy, altylinto, halo, intituorométhyle ou leurs associations) et la portion of a'dralyle set un altyle droit ou ramife ayant 1 à 6 atomes de carbone), ou ben aryle fettur un groupe phényle non substitué ou substitué (où le phényle substitué représente phényle, mono-ou di-substitué par altyle, hydrony, alcoxy, altylinto, halo, intituorométhyle ou leurs associations).

- Composition pharmaceutique comprenant comme ingrédient actif un composé selon l'une quelconque des revendications 1 à 7, avec un support acceptable en pharmacie.
- 20 11. Utilisation d'un composé selon l'une quelconque des revendications 1 à 7, pour la préparation d'une composition pharmaceutique à utiliser pour le traitement des psychloses ou de la dépression ou bien pour effectuer une analgésie, en particulier, pour une utilisation en tant qu'antipsychotique.

Revendications pour l'Etat contractant sulvant : ES

Procédé pour la préparation d'un composé de la formule I

$$R^4$$
 R^5
 R^1
 R^2

et ses sels acceptables en pharmacie, où :

R¹ représente -XR⁵, -CH₂R³, cycloalkyle ayant 3 à 8 atomes de carbone, cycloalcényle ayant 5 à 8 atomes de carbone.

u ovrroivie :

R? représente -H ou bien R¹ et R² représentent ensemble alcanediyle étant une chaîne d'hydrocarbure divalent, droite ou ramifiée ayant 1 à 6 atomes de carbone;

R3 représente H ou un alkyle droit ou ramifié avant 1 à 6 atomes de carbone ;

R⁴ représente H, halo, alivje droit ou ramitié syant 1 à 6 atomes de carbone, haloalivjle étant un alkyle droit ou ramitié ayant 1 à 6 atomes de carbone susbitiué par 1 à 5 groupes halo ou blen alcoxy (où la portion alkyle est un alkyle droit ou ramitié ayant 1 à 6 atomes de carbone);

R5 représente -OR10, -N(R9)2 ou -O.C(R7)2.OCOR13;

If représente H, allyle droit ou ramifé ayant 1 à 6 stomes de carbone, cycloalityle ayant 3 à 8 stomes de carbone, cycloalityle ayant 3 à 8 stomes de carbone, cycloalityle yet of be profit anyle est un phényle non substitué ou substitué ou le phényle substitué représente phényle mon-ou disubstitué par alkyle, hydroxy, alcoxy, altylithi, hab, trilliucomitélyle ou leur associations et la portion altyle est un alkyle droit ou ramifé ayant 1 à 6 atomes de carbone), hétinarylityle (où la portion d'hétinaryle est un alkyle droit ou ramifé ayant 1 à 6 atomes de carbone), hidinarylityle (où la portion d'hétinaryle est un alkyle droit ou ramifé ayant 1 à 6 atomes de carbone), hidinarylityle (où la portion d'hétinaryle est un alkyle droit ou ramifé ayant 1 à 6 atomes de carbone), hidinarylityle (où la portion d'hétinaryle est un alkyle droit ou ramifé ayant 1 à 6 atomes de carbone), hidinarylityle (où la portion alkyle est est un cycloalityle yet où la portion alkyle est est un cycloalityle yet avant 1 à 6 atomes de carbone, cycloalityle yet où la portion alkyle est un cycloalityle yet un alkyle droit ou ramifé ayant 1 à 6 atomes de carbone, cycloalityle yet un alkyle droit ou ramifé d'a bonne de carbone, ou bien alcoxylalyle (où la portion alkyle est un alkyle droit ou ramifé d'a bonne de carbone), cycloalityle (où la portion alkyle est un alkyle droit ou ramifé d'a bonne de carbone, ou bien alcoxylalyle (où la portion alkyle est un alkyle droit ou ramifé ayant 1 à 6 atomes de carbone), cycloalityle (où la portion alkyle est un alkyle droit ou ramifé ayant 1 à 6 atomes de carbone), cycloalityle (où la portion alkyle est un alkyle droit ou ramifé ayant 1 à 6 atomes de carbone), cycloalityle (où la portion alkyle est un alkyle droit ou ramifé ayant 1 à 6 atomes de carbone), cycloalityle (où la portion alkyle est un alkyle droit ou ramifé ayant 1 à 6 atomes de carbone), cycloalityle (où la portion alkyle est un alkyle droit ou ramifé ayant 1 à 6 atomes de carbone), cycloalityle (où la portion alkyle est un alkyle droit ou

R7 représente H ou bien alkyle droit ou ramifié ayant 1 à 6 atomes de carbone;

R¹ représente cyclosityle ayart 3 à 8 atomes de carbone, cyclosidenyle ayart 5 à 8 atomes de carbone, cyclositylatiyle (où 1a portion cyclosityle est un cyclosityle eyart 3 à 8 atomes de carbone et la portion altyle set un altyle troit ou ramifé ayart 1 à 6 atomes de carbone) ou cyclosidenylatiyle (où 1a portion de cyclosidenyle est un cyclosidenyle ayart 5 à 8 atomes de carbone et la portion d'etiyle est un altyle droit ou ramifé ayart 1 à 8 otomes de carbone);

Chaque R² représente indépendamment H, alivje droit ou amilié ayant 1 à 8 etumes de carbone, co joi la portion aité, est un altylé droit ou remifié eyant 1 à 6 atomes de carbone, alcoxyallyle (ob les deux portions alivjées sont des alivjees droits ou ramifiés ayant 1 à 6 atomes de carbone, araityle (ol le portion anyle est un phényle non substitué ou substitué ol le phényle substitué prépésente un phényle mono on d'au-bustitué par alityle, hydroxy, alcyvithe, hale, urituorométryle ou leurs associations et la portion d'alivje est un alivje droit ou ramifié ayant 1 à 6 etomes de actone) ou blen anyle dastu un groupe phényle non substitué ou substitué où le phényle substitué représente un phényle mono- ou di-substitué par alityle, hydroxy, alcoxy, alitylithio, halo, trifluorométhyle ou leurs associations :

R10 représente H, -COR9 ou -CON(R9 > :

R¹³ représente aliquie droit ou ramilié ayant 1 à 6 atomes de carbone, arailysis (où la portion d'arryle set un plénique non substitué ou auxiliaté où la phénige aubstitué représente plénique monor Du disubstitué par aliqvie, hydrory, alcony, aliqvitibo, halo, trittuorendéhyle ou leurs associations et la portion of allayle set un aliqvie droit ou ramilié ayant 1 à 6 atomes de carbons ou bien aryle étant un groupe phénique non substitué ou substitué où le plénique substitué par représente phénique mon ou di-substitué par aliqvie, hydrory, alcony, alivythio, habo, trittuorendéhyle ou leurs associations;

X représente -O- ou -S-;

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m représente 0 ou 1 ;

Y représente N ou CH ;

Z représente CH₂ (si Y ne représente pas CH) ou bien NR²; et chacun de p et q représente indépendamment des nombres entiers de 1 à 3 tels que la somme de p plus q soit comprise entre 1 et 5 et que p et q ne représentent pes tous deux 1 quand Y est N et Z est NR²,

lequel procédé comprend un procédé choisi parmi les procédés A à E suivants :

A : réduction d'un composé carbonyle de la lormule générale :

7

B. réduction d'un ester de la formule générale :

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C : réduction de la double liaison d'un sel de la formule générale :

D : condensation intramoléculaire d'un composé de la formule générale :

avec élimination de HD et formation du noyau d'azépine, E : réduction, à la double liaison oléfinique, d'un composé de la formule générale :

où dans, les formules ci-dessus, la ligne en pointillé dans le noyau d'azépine représente une double ilaison facultative, R¹, R², R³, R⁴ et R²⁰ sont tels que définis à la trevendication 1, R⁴ est R² ou CORI¹, R⁴ est R² le la revendication 1 ou set atorsy (e) la portion d'ablye est un alsyle droit ou ramifié ayant 1 à 6 atomes de carbone), L² est un ainon, de préférence un anion dérivé d'un habeade ou d'un acide sufficique, D est un groupe réactif pouvant être éliminé en tant que DH avec formation du noyau d'adépline et 2 et R² ou R².

ledit procédé étant suivi, si on le souhaite, par une ou plusieurs des étapes facultatives suivantes : (i) élimination de tout groupe protecteur présent à l'atome d'exote,

(ii) alkylation à l'atome d'azote où Ra est hydrogène pour introduire R3 qui est alkyle,

(iii) éthérification ou thioéthérification de R¹ où R¹ est -OH et R² est H pour donner un éther ou thiol correspondant,

(iv) estérification de R5 où R5 est -OH.

(v) halogénation de R* où R* est H.

 (vi) hydroxyméthylation de R⁴ où R⁴ est H, avec ensuite réduction du groupe hydroxyméthyle ainsi introduit en méthyle,

et avant ou après ladite ou lesdites étapes facultatives, désaltylation de R^{5a} où R^{5a} est alcoxy, le composé ainsi obtenu de formule i étant isolé sous forme libre ou blen sous la forme d'un sel acceptable en pharmacie.

- 2. Procédé selon la revendication 1 où R¹ représante -XR⁴, -CN-R⁴, cycloalityle ayant 3 à 8 atomes de carbone ou cycloalicényle ayant 5 à 8 atomes de carbone où X représente -O-, ou -S-, R⁴ représente un allyte droit ou ramifié ayant 1 à 8 atomes de carbone, cycloalityle ayant 3 à 8 atomes de carbone un allyte droit ou ramifié ayant 1 à 8 atomes de carbone, cycloalityle ayant 3 à 8 atomes de carbone droit ou ramifié ayant 1 à 8 atomes de carbone, blaotalityle detau n allyte droit ou ramifié ayant 1 à 6 atomes de carbone, blaotalityle datun a naivige droit ou ramifié ayant 1 à 6 atomes de carbone substitué par 1 à 5 groupes hato ou alcoxy allyte (où les deux portions d'allyte sort des allytes droits ou ramifiés ayant 1 à 6 atomes de carbone et R¹ représente oryctoshtyle ayant 3 à 8 atomes de carbone ou alcoxyalityle (où les deux cortions d'allyte las del des affects de l'arbones de carbone cu alcoxyalityle (où les deux cortions d'allyte sont des allytes droits ou artifiés ayant 1 à 6 atomes de carbone ou alcoxyalityle (où les deux cortions d'allytes sont des allytes droits ou artifiés ayant 1 à 6 atomes de carbone ou alcoxyalityle (où les deux cortions d'allytes sont des allytes droits ou artifiés ayant 1 à 6 atomes de carbone ou alcoxyalityle (où les deux cortions d'allytes sont des allytes droits ou artifiés ayant 1 à 6 atomes de carbone.
 - Procédé selon la revendication 2 où R¹ représente cyclohexyle ou cyclohexényle.
 - 4. Procédé selon la revendication 1, où R¹ représente



ou pyrrolyle où m est 1 et R⁹ représente H, ou bien alkyle droit ou ramifié ayant 1 à 6 atomes de carbone.

- 5. Procédé selon l'une quelconque des revendications précédentes où R3 représente -CH3.
- 6. Procédé selon l'une quellocnique des revendications précédentes où R° noprésente halo, de préférence choire et R° preférente olle, PoCOR° ou -QC(PP), OCOR° où -QC(PP), OCOR° où -QC(PP) et présentes altiglés de droi ou ramifié ayant 1 à 6 atomes de carbonn, alcoxy (cò la portion d'altyle est un altyle droit ou ramifié ayant 1 à 6 atomes de carbonn) ou alcoxyleify (cò las destupe profins d'altyles sont des altyles droits ou ramifiés ayant 1 à 6 atomes de carbonn).
- 7. Procédé selon la revendication 1, où le composé produit est choisi parmi :

 8-chioro-5-méthoxy-3-méthyl-2a,45-étrahydro-1H-3-benzazépine-7-ol,
 8-chioro-5-étroxy-3-méthyl-2a,45-étrahydro-1H-3-benzazépine-7-ol,
 8-chioro-5-étroy-1-méthyl-2a,45-étrahydro-1H-3-benzazépine-7-ol,
 8-chioro-3-méthyl-5-(1-pipéridinyl-2a,45-étrahydro-1H-3-benzazépine-7-ol,

 8-chioro-5-cyclchosyl-3-méthyl-2a,45-étrahydro-1H-3-benzazépine-7-ol,
 8-chioro-5-cyclchosyl-3-méthyl-2a,45-étrahydro-1H-3-benzazépine-7-ol,
 8-chioro-5-cyclchosyl-3-méthyl-2a,45-étrahydro-1H-3-benzazépine-7-ol,
 8-chioro-5-cyclchosyl-3-méthyl-2a,45-étrahydro-1H-3-benzazépine-7-ol,
 8-chioro-5-cyclchosyl-3-méthyl-2a,45-étrahydro-1H-3-benzazépine-7-ol,
 8-chioro-5-benzylon-3-méthyl-2a,45-étrahydro-1H-3-benzazépine-7-ol,
 8-chioro-5-benzylon-3-méthyl-2a,45-étrahydro-1H-3-benzazépine-7-ol,
 8-chioro-5-benzylon-3-méthyl-2a,45-étrahydro-1H-3-benzazépine-7-ol,
 8-chioro-5-(p-mynyl-3)-méthyl-2a,45-étrahydro-1H-3-benzazépine-7-ol,
 8-chioro-5-(p-mynyl-3)-méthyl-2a,45-étrahydro-1H-3-benzazépine-7-ol,
 8-chioro-5-(p-mynyl-3)-méthyl-2a,45-étrahydro-1H-3-benzazépine-7-ol,

8-chior-7-khydroxy-3-m6thy+2.3.4,5-lifetahydro-spiro [1H-3-benzazápine-5,5'-cyclopentane], 8-chior-7-(kihoxy-formyloxy)-5-cyclohoxyl-3-m6thy+2.3.4,5-lifetahydro-1H-3-benzazápine, 8-chior-7-(sporpy-formyloxy)-5-allyl-3-m6thy+2.3.4,5-lifetahydro-1H-3-benzazápine, 8-chior-7-ackioxy-5-di-m8thy-2-bidhy-3-m6thy+2.3.4,5-lifetahydro-1H-3-benzazápine, 8-chior-7-y-Chydroxy-form8thy-2-bidhy-3-m6thy+2.3.4,5-lifetahydro-1H-3-benzazápine, 8-chior-7-(b-bityroxy-m6thoxy)-5-allyl-3-m6thy+2.3,4-5-lifetahydro-1H-3-benzazápine, et las selá sozotables en ordamzáne do eo au indfebble en benzazápine,

8. Procédé pour la préparation d'un composé de la formule !!

et ses sels acceptables en pharmacie, où :

Q représente H. halo ou -SO₂R" où R" est CH₂, CF₃, phényle ou tolvie :

R³² représants H, allyte droit ou ramifé ayant 1 à 6 alones de carbone ou COOR¹⁴ où R¹⁴ est daily droit ou armifé ayant 1 à 6 alones de carbon, ayré étant un group péthyle non substitué ou substitué do phényle substitué représante phényle mono- ou di-aubstitué par airyle, hydroxy, alcoxy, aldaylitho, hab, triturorchityle ou leur sassociations, arallyle (ou la portion d'aryle est un pényle mono- ou di-aubstitué par airyle, hydroxy, alcoxy, albertyle substitué ou substitué où la phényle mono- ou di-aubstitué par airyle, phydroxy, alcoxy, allytthio, hab, rithromedityle ou leur associations est la portion d'airyle est un airyle droit ou ramifé ayant 1 à 6 atomes de carbone) ou habaltyle, étant un airyle droit ou ramifé ayant 1 à 6 atomes de carbone) ou babaltyle, étant un airyle droit ou ramifé ayant 1 à 6 atomes de carbone substitué ou 1 à 5 orruppes hab.

R¹ représente H, halo, alkyle droit ou ramifié eyent t à 6 atomes de carbone, haloalkyle étant un alkyle droit ou ramifié ayant, 1 à 6 atomes de carbone substitué par 1 à 5 groupes halo ou bien elcoxy (où la portion d'alkyle est un alkyle droits ou ramifié ayant 1 à 6 atomes de carbone);

 R^{4a} représente $-OR^{1o}$, $-N(R^{4})_{2}$, $-O.C(R^{2})_{2}$, $OCOR^{1o}$ ou alcoxy (où la portion alkyle est un alkyle droit ou ramifié ayant 1 à δ atomes de carbone); où R^{2} représente H, ou un alkyle droit ou ramifié ayant 1 à δ atomes de carbone :

chaque. Pr exprésente indépendamment H, un altyte droit ou ramilés ayant 1 à 8 atomes de carbone, alcony (où la portion d'alloyte est un altyte droit ou ramilés ayant 1 à 6 atomes de carbone); alcoxyaltyle (où las deux portions d'alloyte sont does altytes droits ou ramiliés eyant 1 à 6 atomes de carbone), araillyle (où la portion d'aryte est un priérriyle non substitué ou sessible d'ou le prérie provise substitué orgateries pétreyle mone ou d'autosited per altyle, hydroxy, alcoxy, altylythot, halo, trillozométryle ou leurs associations et la portion d'altyle est un altyle droit ou ramilié eyent 1 à 6 atomes de carbone) ou aryle étant un groupe pétreyle non substitué orgatement pétreyle mone ou di-substitué par altyle, hydroxy, alcoxy, altylithò, halo, trillozométryle ou leurs associations, Rife recertament H. COPP ou -COMIRP»; et

R¹³ aprésante alixije droit ou ramillé ayant 1 à 6 atomes de carbone, arailyris (où e portion d'aryis est un phénip non substitué ou substitué (où le phénip substituit prespésant un phéniple non-co ud substitué par alixije, hydroxy, aloxy, alixylitis, hab, trillucomethyle ou leura sesociations) et le portion d'attiye set un alixyle droit ou ramille dyant 1 à 6 atomes de carbone), ou bien aryis élart un groupe phényle non substitué ou substitué (où le phényle substitué représente phényle, mono- ou di-substitué par alixyle, hydroxy, aloxy, alixylitis, hub, trillucométhyle ou leura sesociations).

lequel procédé comprend l'halogénation du composé de formule VIII :

- 10 pour donner un composé de formule II ou Q représente halo ; et l'hydrolyse subséquente en un groupe OH et la réaction avec un halogénure de suitonyle ou un anhydride pour donner un composé de la formule II to Q est -OSO,RP.
 - Procédé de préparation d'une composition pharmaceutique qui comprend le mélange, en tant qu'ingrédient actif, d'un composé préparé seton l'une quelconque des revendications 1 à 7 avec un support en pharmacie.

Revendications pour l'Etat contractant sulvant : GR

20 1. Composé ayant la formule de structure I

et ses sels acceptables en pharmacie, où :

R¹ représente -XR⁵, -CH₂R⁵, cycloalkyle ayant 3 à 8 atomes de carbone, cycloalcényle ayant 5 à 8 atomes de carbone.

ou pyrrolyle ;

35

R² représente -H ou bien R¹ et R² représentent ensemble alcanediyle étant une chaîne d'hydrocarbure divanient, droite ou ramifiée ayant 1 à 6 atomes de carbone ;

R3 représente H ou un alkyle droit ou ramifié ayant 1 à 6 atomes de carbone ;

R⁴ représente H, halo, alivjle droit ou ramilié ayant 1 à 6 atomes de carbone, haloalikyle étant un alivjle droit ou ramilié ayant 1 à 6 atomes de carbone sustritué par 1 à 5 groupes halo ou blen alcoxy (où la portion alivjle est un alivjle droit ou ramilié ayant 1 à 6 atomes de carbone);

R5 représente -OR10, -N(R9 2 ou -O.C(R7 2.OCOR13;

Rf 'rgordsente H, allyle droit ou ramifié syant 1 à 8 atomes de carbone, cycloalityle syant 3 à 8 atomes de carbone, cycloalityle syant 3 à 8 atomes de carbone, cycloalityle syant 3 à 8 atomes de carbone, arbyle (obl à portion argive st un phényle non substitué ou substitué où le phényle substitué représents prényle mono- ou di-substitué par allyle, hydroxy, alcoyx, altylithe, halo, trituorométhyle ou leurs associations et la portion altyle un alkyle droit ou armifié syant 1 à 6 atomes de carbone, hétérosylealyle (où la portion of hétérosyle est un altyle droit ou ramifié syant 1 à 6 atomes de carbone, háterosyle faut un altyle droit ou ramifié syant 1 à 6 atomes de carbone, háterosyle faut un altyle droit ou ramifié syant 1 à 6 atomes de carbone, háterosyle faut un altyle droit ou ramifié syant 1 à 6 atomes de carbone, háterosyle faut un altyle droit ou ramifié syant 1 à 6 atomes de carbone, háterosyle faut un altyle droit ou ramifié

ayant 1 à 8 atomes de carbone substitué par 1 à 5 groupes halo, altérhyte droit ou ramifié ayant 1 à 6 atomes de carbone, ellrynýte syart 2 à 6 atomes de carbone, cycloallypiely 60 la portion cycloallypie est un cycloallyfe ayant 3 à 8 atomes de carbone et la portion altyle est un altyle droit ou ramifié eyant 1 à 8 atomes de carbone, cycloallyfallybie (00 la portion cycloallériyie est un cycloallériyie ayant 5 à 8 atomes de carbone et la portion altyle est un altyle droit ou armifié ayant 1 à 8 atomes de carbone, cycloalleriye (00 les deux portions altyles sont des altyles droits ou ramifiés ayant 1 à 8 atomes de carbone);

R7 représente H ou bien alkyle droit ou ramifié ayant 1 à 6 atomes de carbone ;

R[®] représente cycloalityle ayant 3 à 8 atomes de carbone, cycloalcényle ayant 5 à 8 atomes de et la portion altyle et la latine cycloalityle est un cycloalityle ayant 3 à 8 atomes de carbone et la portion altyle est un altyle droit ou ramifé ayant 1 à 8 atomes de carbone) ou cycloalcényle latine (où la portion de cycloalcényle est un cycloalcényle eyant 5 à 8 atomes de carbone et la portion d'altive les tun altive droit ou ramifé ayant 1 à 8 atomes de carbone).

Chaque PF représente indépendamment H, allyle droit ou ramifié ayant 1 à 6 atomes de carbone, alcony (où la portion alique et un allyle droit ou ramifié ayant 1 à 6 atomes de carbone, lacovajkily et où les deux portions aliques sont des allyles droits ou ramifiés ayant 1 à 6 atomes de carbone, aralique (où la portion aryle est un phényle non substitué ou substitué où la préhip substitué présente un phényle monre- ou d'au-bustitué par altyle, hydroxy, alcoxy, ellythino, halo, trifluorométhyle ou leurs associations et la portion d'allyle est un altyle droit ou ramifié ayant 1 à 8 demandes carbone) ou bien anyle étant un group préhip les nou substitué ou substitué par altyle, hydroxy, alcoxy, alkylthio, halo, trifluorométhyle ou leurs associations ;

R10 représente H. -COR9 ou -CON(R9):

Pl' représente albyte d'ordi ou ramilié ayant 1 à 6 atomes de carbone, araillyte (où la portion d'aryis et un phérijne non substitué ou la phérijne substitué oil parfiyre substitué représente phérijne monc ou disubstitué par allyris, hydroxy, aboxy, albythio, halo, tritlorométhyle ou leurs associations et la portion of d'albyte est un allyre dord ou ramilié ayant 1 à 6 atomes de carbone) ou blen aryis étant un groupe puphérijne non substitué ou substitué où le phériyle substitué représente phérijn mono ou di-substitué par silvide. hydroxy, calarox, elabythio, hob, tritlavométhyle ou leurs associations :

X représente -O- ou -S- ;

m représente 0 ou 1 ;

Y représente N ou CH;

Z représente CH2 (si Y ne représente pas CH) ou bien NR9; et

chacun de p et q représente indépendamment des nombres entiers de 1 à 3 tels que la somme de p plus q soit comprise entre 1 et 5 et que p et q ne représentent pas tous deux 1 quand Y est N et que . Z est NR^a.

- 2. Composé selon la mienedication 1 où RI reportisente. XFR, -CH₂RP, cycloalityle ayant 3 à 8 etomes de carbone où X repóstente-On ou S-, RF représente un alkyle droit ou ramifié ayant 1 à 6 atomes de carbone, cycloalityle ayant 3 à 8 atomes de carbone, arakyle (où la portion aryle set un prévie non substituté ou substituté et la portion alkyle et droit ou ramifié ayant 1 à 6 atomes de carbone, hacistiyé de faut ma alkyle droit ou ramifié ayant 1 à 6 atomes de carbone, hacistiyé de faut ma alkyle droit ou ramifié ayant 1 à 6 atomes de carbone substituté par 1 à 5 groupes halo ou aboxy alkyle (où les deux portions d'alkyle sont des alkyles droits ou ramifié ayant 1 à 6 atomes de carbone et RF repésente l'explaiklys et avait à l'alkyle avant 5 à 6 atomes de carbone ou aboxyalkyle (où les deux portions d'alkyles sont des alkyles droits ou ramifiés ayant 1 à 6 atomes de carbone ou aboxyalkyle (où les deux portions d'alkyles sont des alkyles droits ou ramifiés ayant 1 à 6 atomes de carbone.
- 3. Composé selon la revendication 2 où R1 représente cyclohexyle ou cyclohexényle.
- so 4. Composé selon la revendication 1, où R1 représente

ou pyrrolyle où m est 1 et ${\rm R}^3$ représente H, ou bien alkyle droit ou ramifié eyant 1 à 6 atomes de carbone.

- Composé selon l'une quelconque des revendications précédentes où R3 représente CH3.
- 6. Composé aelon l'une quelconque des revendications précédentes oû R° représente halo, de préférence chiore et R° représente -01. COCR° ou -0.0(P), DCCR° où 60° représente et l'able de cit ou ramifé ayant 1 à 6 atomes de carbone, abcosy (eò la portion d'allyle est un allyle droit ou ramifé ayant 1 à 6 atomes de carbone), autocorylatyle (où las deux portions d'allyless sont des allyles circits ou ramifés ayant 1 à 6 atomes de carbone). R° représente H et R¹º représente un allyle droit ou ramifé ayant 1 à 6 atomes de carbone.
- 7. Composé salon la revendication 1, ledit composé étant choisi parmi : 8-Chloro-5-méthoxy-3-méthyl-2.3.4.5-tétrahydro-1H-3-benzazépine-7-ol. B-Chloro-5-éthoxy-3-méthyl-2,3,4,5-tétrahydro-1H-3-benzazépine-7-ol, 8-chloro-5-éthylthio-3-méthyl-2,3,4,5-tétrahydro-1H-3-benzazépíne-7-ol, 7-Chloro-8-diméthylcarbamoyl-1-éthoxy-méthyl-2,3,4,5-tétrahydro-1H-3-benzazépine, 8-chloro-3-méthyl-5-(1-pipéndinyl)-2,3,4,5-tétrahydro-1H-3-benzazépine-7-ol, 8-Chloro-5-cyclohexyl-3-méthyl-2.3.4.5-tétrahydro-1H-3-benzazépine-7-ol. 8-chtoro-5-cyclohexyloxy-3-méthyl-2,3,4,5-tétrahydro-1H-3-benzazépine-7-ol, 8-chloro-5-(2-cyclohexényl)-3-méthyl-2,3,4,5-tétrahydro-1H-3-benzazépine-7-ol, 8-Chloro-5-allyl-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine-7-ol, 8-chloro-5-(2,2,2-trifluoroéthoxy)-3-méthyl-2,3,4,5-tétrahydro-1H-3-benzazépine-7-ol, 8-chloro-5-benzyloxy-3-méthyl-2,3,4,5-tétrahydro-1H-3-benzazépine-7-ol, 8-Chloro-5-(phénéthyloxy)-3-méthyl-2,3,4,5-tétrahydro-1H-3-benzazépine-7-ol, 8-chloro-5-(1-pyrrolyl)-3-méthyl-2,3,4,5-tétrahydro-1H-3-benzazépine-7-ol, 8-chloro-7-hydroxy-3-méthyl-2.3.4.5-tétrahydro-spiro [1H-3-benzazépine-5,5'-cyclopentane], 8-chloro-7-(éthoxy-formyloxy)-5-cyclohexyl-3-méthyl-2,3,4,5-tétrahydro-1H-3-benzazépine, 8-Chloro-7-(isopropyl-formyloxy)-5-allyl-3-méthyl-2,3,4,5-tétrahydro-1H-3-benzazépine, 8-chloro-7-(méthoxy-acétoxy)-5-allyl-3-méthyl-2,3,4,5-tétrahydro-1H-3-benzazépine, B-chloro-7-acétoxy-5-(3-méthyl-2-butényl)-3-méthyl-2,3,4,5-tétrahydro-1H-3-benzazépine, 8-chloro-7-(t-butyroxy-méthoxy)-5-allyl-3-méthyl-2,3,4,5-tétrahydro-1H-3-benzazépine, et les sels acceptables en pharmacie de ce qui précède.
- 38 8. Procédé pour la préparation d'un composé de la formule I selon la revendication 1, lequel procédé comprend un procédé choisi par les procédés A à E qui subvuel s'air à réduction d'un composé carbonyle de la formule générale :

B. réduction d'un ester de la formule générale :

C : réduction de la double liaison d'un sel de la formule générale :

D : condensation Intramoléculaire d'un composé de la formule générale :

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avec élimination de HD et formation du noyau d'azépine, E : réduction,à la double liaison oléfinique, d'un composé de la formule générale :

où, dans les formules ci-dessas, la ligne en pointillé dans le noyau d'azépine représente une ouble liaion tacutière, R.P. R.P. et et Pa son thes que définé à la revendication 1, 4º est R l'ou COOR³, Ré est R let que définé à la revendication 1 ou est aloxy (où la portion d'allyté est un aivid, est perférence un ainon deriré d'un haloacide ou d'un acid sautionique, D est un groupe résetif pouvant être éliminé en tant que DH avec formation du nova d'asépine et c et et R ou R³.

ledit procédé étant suivi, si on le souhaite, par une ou plusieurs des étapes facultatives suivantes :
(i) élimination de tout groupe protecteur présent à l'atome d'azote.

(ii) alkylation à l'atome d'azote où Ro est hydrogène pour introduire R3 qui est alkyle,

(iii) éthérification ou thioéthérification de R1 où R1 est -OH et R2 est H pour donner un éther ou thiol correspondant,

(iv) estérification de R5 où R5 est -OH,

(v) halogénation de R⁴ où R⁴ est H .

(vi) hydroxyméthylation de R⁴ où R⁴ est H, avec ensuite réduction du groupe hydroxyméthyle ainst introduit en méthyle.

et avant ou après ladite ou lesdites étapes facultatives, désalkylation de R5a où R5a est alcoxy.

le composé ainsi obtenu de formule I étant isolé sous forme libre ou bien sous la forme d'un sel acceptable en pharmacie.

. Composé de la formule II

et ses sels ecceptables en pharmacie, où :

Q représente H, halo ou -SO2R" où R" est CH2, CF2, phényle ou tolyle ;

R³⁶ représente H, allyle droit ou ramifié ayant 1 à 6 stomes de carbone ou COOR¹⁴ où R¹⁶ est aligh droit ou ramifié ayant 1 à 6 stomes de carbone, ayré dath un groupe phérinje non substitué ou substitué où pitérnyle substitué représente phérinje mono- ou d'autsetitué par allyle, hydroxy, atcoxy, attythic, hajs, tilmournethlyle ou lours associations, arallyle (ou la portion d'aryle est un phériyle non substitué ou substitué où le phérnyle substitué représente phérinje mono-ou di-substitué par ellyle, hydroxy, elocxy, silyrithio, halo, tilmournethlyle ou luva associations et la portion d'allyle est un alkyle droit ou ramifié ayant 1 à 8 atomes de carbone) ou halostkyle, étant un ellyle droit ou ramifié ayant 1 à 6 etomes de carbone substitué par 1 à 8 groupes halo

R* représente H, halo, alkyle droit ou ramifié ayant 1 à 6 atomes de carbone, haloalkyle étant un alkyle droit ou ramifié ayant 1 à 6 atomes de carbone substitué par 1 à 5 groupes halo ou bien alcoxy (où la nortino d'alkyle est un alkyle droite ou ramifié ayant 1 à 6 atomes de carbone):

R^{2a} représente -OR^{1o}, -N(R²)_b, -O.C(R²)_b, OCOR¹⁵ ou atcoxy (cù la portion alkyle est un alkyle droit ou ramilié ayant 1 à 8 etomes de carbone); où R² représente H, ou un alkyle droit ou ramilié ayant 1 à 6 atomes de carbone :

chaque IP représente indépendamment II, un alkyle droit ou ramifé syant 1 à 6 atomes de carbone, alcoxy (où la portion d'alkyle est un alkyle droit ou ramifé syant 1 à 6 atomes de carbone), active (où la portion d'alkyle est un alkyle droit ou ramifé syant 1 à 6 atomes de carbone), arakyle (où la portion d'arlyle est un phirtyle non substitut ou substitut do la phényle substitut représente prényle mone- ou d'autyle sit on privaty le substituté par alkyle, hydroxy, alcoxy, allythio, habo, trittorométhyle or lutre associations et la portion d'alkyle est un alkyle droit ou ramifé syant 1 à 6 atomes de carbone) ou aryle étant un groupe piényle non substitué ou substituté représente phényle mone- ou d'autylettus par alkyle, lutroxy, elocoxy, ellythio, habo, trittorométhyle ou leur associations,

R10 représente H, -COR9 ou -CON(R9)2 ; et

R¹¹ apprisente aliyle diroit ou ramifié syent 1 à 6 stomes de carbons, arallyle (où la portion d'aryle set un phéryle non substitut do 10 phéryles abstitut représente un phéryle morro- ou disubstitut par altyle, hydroxy, alcoys, alivylinio, halo, titiliorométhyle ou leurs associations) et la portion d'altyle est un alivyle droit ou ramifié ayant 1 à 8 almes de carbono, ou bien aryle festim un grouppe phéryle non substitut de substitut (où le phéryle substitut eropé-certain phéryle, mone- ou di-substitut qua alivyle, hydroxy, elcoxy, elcoytinio, hole, tritiliorométhyle ou leurs associations).

 Procédé de préparation d'une composition pharmaceutique qui comprend le mélange, comme ingrédent actif, d'un composé selon l'une quelconque des revendications 1 à 7, avec un support acceptable en pharmarie

Utilisation d'un composé selon l'une quelconque des revendications 1 à 7, pour la préparation d'une
composition pharmaceutique à utiliser pour le traitement des psychloses ou de la dépression ou bien
pour effectuer une analgésie, en particulier, pour une utilisation en tant qu'antipsychotique.